(FILE 'HOME' ENTERED AT 11:41:31 ON 02 OCT 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 11:41:57 ON 02 OCT 2003
L1 3471 S IL4
L2 69533 S INTERLEUKIN4 OR "INTERLEUKIN 4"
L3 70329 S L1 OR L2
L4 413 S PTH-RP
L5 416688 S PROMOTER
L6 0 S L3 AND L4 AND L5
L7 2 S PTH-RP AND PROMOTER
L8 2 DUP REM L7 (0 DUPLICATES REMOVED)
L9 7232 S PTHRP
L10 7616 S L9 OR L4
L11 225 S L10 AND GENE EXPRESSION AND PROMOTER
L12 0 S L11 AND L2
L13 524813 S INTERLEUKIN
L14 69531 S L2 AND L13
L15 4 S L11 AND L13
L16 2 DUP REM L15 (2 DUPLICATES REMOVED)
L17 1782 S HHM OR (HUMORAL HYPERCALCEMIA OF MALIGNANCY)
L18 45 S L11 AND L17
L19 16 DUP REM L18 (29 DUPLICATES REMOVED)

=> d l19 ibib ab 1-
YOU HAVE REQUESTED DATA FROM 16 ANSWERS - CONTINUE? Y/(N):y

L19 ANSWER 1 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2002678469 MEDLINE
DOCUMENT NUMBER: 22326517 PubMed ID: 12438453
TITLE: Guanosine nucleotides inhibit different syndromes of ***PTHrP*** excess caused by human cancers in vivo.
COMMENT: Comment in: J Clin Invest. 2002 Nov;110(10):1399-401
AUTHOR: Gallwitz Wolfgang E; Guise Theresa A; Mundy Gregory R
CORPORATE SOURCE: OsteoScreen Ltd., San Antonio, Texas 78229, USA.. gallwitz@osteoscreen.com
CONTRACT NUMBER: P01CA40035 (NCI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (2002 Nov) 110 (10) 1559-72.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021120
Last Updated on STN: 20030202
Entered Medline: 20030131
AB There are two well-described syndromes caused by tumor production of parathyroid hormone-related peptide (***PTHrP***), namely osteolytic bone disease associated with breast cancer and ***humoral*** ***hypercalcemia*** of ***malignancy*** (***HHM***) that occurs with or without bone metastasis. Both syndromes have been shown experimentally to be inhibited by neutralizing antibodies to ***PTHrP*** . In a search for small-molecule inhibitors of ***PTHrP*** production or effects, we have identified guanine-nucleotide analogs as compounds that inhibit ***PTHrP*** expression by human tumor cells associated with these syndromes. We show in nude athymic murine models that these compounds reduce ***PTHrP*** -mediated osteolytic lesions associated with metastatic human breast-cancer cells as well as the degree of hypercalcemia caused by excessive ***PTHrP*** production by a squamous-cell carcinoma of the lung. These results suggest that the ***PTHrP*** gene ***promoter*** may be a suitable target for treating the skeletal effects of malignancy.

L19 ANSWER 2 OF 16 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2001061792 MEDLINE
DOCUMENT NUMBER: 20500859 PubMed ID: 11044652

L8 ANSWER 1 OF 32 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2003209723 EMBASE
TITLE: New ***vitamin*** ***D*** ***analogs*** .
AUTHOR: Slatopolsky E.; Finch J.; Brown A.
CORPORATE SOURCE: Dr. E. Slatopolsky, Renal Division, Box 8126, Department of Internal Medicine, 660 S. Euclid Ave., St. Louis, MO 63110, United States. Eslatopo@im.wustl.edu
SOURCE: Kidney International, Supplement, (2003) 63/85 (S83-S87).
Refs: 29
ISSN: 0098-6577 CODEN: KISUDF
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 003 Endocrinology
028 Urology and Nephrology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background. 1,25-(OH)(2)D(3) (calcitriol) controls parathyroid gland growth and suppresses the synthesis and secretion of parathyroid hormone. Because of this, 1,25-(OH)(2)D(3) has been used successfully for the treatment of secondary hyperparathyroidism, which almost always accompanies renal failure. However, the potent effect of 1,25-(OH)(2)D(3) on intestinal calcium and phosphorus absorption and bone mineral mobilization often leads to the development of hypercalcemia and hyperphosphatemia precluding 1,25-(OH)(2)D(3) therapy. Methods. This has led to the development of ***vitamin*** ***D*** ***analogs*** that retain the suppressive action on ***PTH*** and parathyroid gland growth, but that have less calcemic and phosphatemic activity. Currently, two ***analogs*** , 19-nor-1,25-(OH)(2)D(2) and 1,.alpha.(OH)D(2), are being used for the treatment of secondary hyperparathyroidism in the United States, and two are being used in Japan, 22-oxa-calcitriol and 1,25-(OH)(2)-26,27F6 D(3). Results. All four ***analogs*** suppressed ***PTH*** , but had less calcemic and phosphatemic activity than 1,25-(OH)(2)D(3). In rats, 19-nor-1,25-(OH)(2)D(2) has been shown to be less calcemic and phosphatemic compared to 1,.alpha.(OH)D(2). Conclusion. Therapeutic doses of 19-nor-1,25-(OH)(2)D(2) could produce a lower Ca x P product compared to 1,.alpha.(OH)D(2), which could be an important consideration in patient treatment. Further studies are necessary to define these differences and to understand the mechanisms behind the differential actions of ***vitamin*** ***D*** ***analogs*** .

L8 ANSWER 2 OF 32 MEDLINE on STN
ACCESSION NUMBER: 2003320413 IN-PROCESS
DOCUMENT NUMBER: 22733976 PubMed ID: 12851915
TITLE: [Treatment of secondary hyperparathyroidism: new pharmacologic approaches]. Meccanismi dell'osteodistrofia uremica e prevenzione dell'iperparatiroidismo del soggetto uremico.
AUTHOR: Brancaccio D; Cozzolino M; Galassi A; Bellasi A; Carpani P; Gallieni M
CORPORATE SOURCE: Divisione di Nefrologia e Dialisi, Ospedale San Paolo, Milano, Italy.. diego.brancaccio@tiscalinet.it
SOURCE: G Ital Nefrol, (2003 May-Jun) 20 Suppl 22 S12-6.
Journal code: 9426434. ISSN: 0393-5590.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Italian
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030710
Last Updated on STN: 20030815
AB The management of secondary hyperparathyroidism is of crucial importance in the treatment of end stage renal disease (ESRD) patients. In particular, hypercalcemia, hyperphosphatemia, and elevated calcium x phosphate (Ca x P) product should be taken into consideration during administration of ***vitamin*** ***D*** metabolites for the

control of ***PTH*** secretion. During the last 10 years, many authors have been studying the efficacy of new non-calcemic ***vitamin*** ***D*** ***analogs*** on suppressing secondary hyperparathyroidism in ESRD patients. In this brief review, we analyzed three new ***vitamin*** ***D*** ***analogs*** : ***22*** - ***oxacalcitriol*** (Maxacalcitriol), 19-nor-1a, 25(OH)2D2 (Paracalcitriol), and 1a (OH)2D2 (Doxacalciferol). In addition, calcimimetic agents may represent a new pharmacologic choice to the treatment of secondary hyperparathyroidism, binding parathyroid calcium sensing receptors (CaSR) and reducing ***PTH*** secretion. These compounds may represent an important tool for the treatment of both secondary hyperparathyroidism and soft tissue calcifications in ESRD patients. In conclusion, a combined use of non calcemic phosphate binders, new ***vitamin*** ***D*** ***analogs*** and calcimimetics should be seriously considered to further improve the already known therapy of secondary hyperparathyroidism in ESRD patients.

L8 ANSWER 3 OF 32 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:574194 CAPLUS
DOCUMENT NUMBER: 137:346302
TITLE: Renal failure and ***vitamin*** ***D***
AUTHOR(S): Brown, Alex J.; Dusso, Adriana S.; Slatopolsky, Eduardo
CORPORATE SOURCE: Renal Division, Washington University School of Medicine, USA
SOURCE: Clinical Calcium (2002), 12(6), 711-723
CODEN: CLCCEJ; ISSN: 0917-5857
PUBLISHER: Iyaku Janarusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review. Secondaly hyperparathyroidism (2HPT), a common disorder in patients with chronic renal failure, develops in response to phosphate retention and low serum 1,25-dihydroxyvitamin D3 [1,25(OH)2D3, calcitriol]. Replacement therapy with calcitriol or its precursor 1 .alpha.-hydroxyvitamin D3 [1.alpha.(OH) D3, alfacalcidol] often produces hypercalcemia and hyperphosphatemia in these patients. Several ***vitamin*** ***D*** ***analogs*** have been developed that retain the direct suppressive action of 1,25 (OH)2D3 on the parathyroid glands but have less calcemic activity, therapy offering a safer and more effective means of controlling 2HPT. 1,25-Ddihydroxy-19-norvitamin D2 (19-nor D2) and 1 .alpha.-hydroxyvitamin D2 (1 .alpha. OHD2) are available in the United States and 1,25-dihydrox-22-oxavitamin D3(***22*** - ***oxacalcitriol*** , OCT) and 1,25-dihydroxy-26,26,26,27,27,27-hexafluoro-vitamin D3 [1,25 (OH)226,27F6D3, falecalcitriol] have been approved for use in Japan. Animal studies have demonstrated that OCT and 19-nor D2 have a wider therapeutic window for suppression of parathyroid hormone (***PTH***) because of their lower calcemic activities of OCT has been attributed to its rapid clearance which prevents sustained effects on intestinal calcium absorption and bone resorption, but still allows a prolonged suppression of ***PTH*** gene expression and parathyroid cell growth. The calcemic activity of 19-norD2 diminishes with the duration of treatment by as yet unknown mechanisms. The lower toxicity of 1 .alpha. OHD2, compared 1 .alpha. OHD3, has also been noted with chronic, but not acute administration, perhaps due to differential metab. The unique actions of falecalcitriol may also result from altered metab. A clear understanding of the mol. basis for the selectivity of ***vitamin*** ***D*** ***analogs*** on parathyroid function may allow the design of even more effective ***analogs*** .

L8 ANSWER 4 OF 32 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002319628 EMBASE
TITLE: Use of ***vitamin*** ***D*** ***analogs*** in chronic renal failure.
AUTHOR: Kim G.; Sprague S.M.
CORPORATE SOURCE: S.M. Sprague, Division of Nephrology, Northwestern University Med. School, Evanston Northwestern Healthcare,

2650 North Ridge, Evanston, IL 60201, United States.
ssprague@northwestern.edu
SOURCE: Advances in Renal Replacement Therapy, (2002) 9/3 (175-183).
Refs: 64
ISSN: 1073-4449 CODEN: ARRTFU
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
028 Urology and Nephrology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Renal osteodystrophy is the term used to describe the spectrum of bone diseases associated with chronic renal failure. Deficiency of 1,25-dihydroxycholecalciferol (calcitriol) plays a major role in the development of renal osteodystrophy, in particular the evolution of secondary hyperparathyroidism. In recent decades, our understanding of the complex interactions between calcium, phosphorus, ***vitamin*** ***D*** , and parathyroid hormone (***PTH***) has increased, resulting in a rational approach to therapy in which ***vitamin*** ***D*** ***analogs*** have become an essential component. The initial ***vitamin*** ***D*** ***analogs*** that have been in widespread clinical use include calcitriol (1,25-[OH](2)D(3)) and alfacalcidol (1.alpha.-[OH]D(3)). These agents have been extensively studied to optimize their effects on secondary hyperparathyroidism. The occurrence of significant hypercalcemia and hyperphosphatemia limiting their use has led to the development of alternative ***vitamin*** ***D*** ***analogs*** that effectively reduce ***PTH*** secretion without causing these complications. Recently, 3 such ***analogs*** , 22-oxa-1,25-(OH)(2)D()3 (OCT), 1.alpha.-(OH)D(2) (doxercalciferol), and 19-nor-1,25-(OH)(2)D(2) (paricalcitol), have been released for clinical use. Only paricalcitol has been studied in comparative human clinical trials with calcitriol in dialysis patients. Preliminary findings suggest a clinical advantage over calcitriol, however, analysis of the larger comparative studies are forthcoming.

L8 ANSWER 5 OF 32 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 1
ACCESSION NUMBER: 2002044564 EMBASE
TITLE: ***Vitamin*** ***D*** ***analogs*** for the treatment of secondary hyperparathyroidism.
AUTHOR: Slatopolsky E.; Brown A.J.
CORPORATE SOURCE: Dr. E. Slatopolsky, Washington Univ. School of Medicine, Renal Division, Box 8126, 660 South Euclid Avenue, St. Louis, MO 63110, United States. eslatopo@im.wustl.edu
SOURCE: Blood Purification, (2002) 20/1 (109-112).
Refs: 15
ISSN: 0253-5068 CODEN: BLPUDO
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Calcitriol controls parathyroid gland (PTG) growth and suppresses the synthesis and secretion of ***PTH*** . However, because of its potent effects on intestinal calcium and phosphorus absorption and bone mobilization, calcitriol treatment can induce hypercalcemia and hyperphosphatemia often precluding its use at therapeutic doses. In the past decade, several ***vitamin*** ***D*** ***analogs*** have been developed. These ***analogs*** retain the action on the PTG while

having less effect on calcium and phosphorus. Most of these ***analogs*** for the treatment of secondary hyperparathyroidism (SH) have a modification on the side chain of calcitriol. In the USA, two ***vitamin*** ***D*** ***analogs*** 19-nor 1,25(OH)(2)D(2) and 1.alpha.(OH)D(2) are currently used for the treatment of SH. Studies in animals demonstrated that 19-nor-1,25(OH)(2)D(2) is less calcemic and phosphatemic than 1.alpha.(OH)D(2). The lower Ca x P product in 19-nor-1,25(OH)(2)D(2)-treated rats may be an important consideration in patient therapy. Further studies in patients are necessary to define these differences.

L8 ANSWER 6 OF 32 MEDLINE on STN
ACCESSION NUMBER: 2003008896 MEDLINE
DOCUMENT NUMBER: 22403119 PubMed ID: 12515379
TITLE: Bone disease in uremic patients: advances in ***PTH*** suppression.
AUTHOR: Brancaccio Diego; Cozzolino Mario; Gorio Alfredo; Di Giulio Anna Maria; Gallieni Maurizio
CORPORATE SOURCE: Nephrology and Dialysis Department, Ospedale San Paolo, Milan, Italy.. diego.brancaccio@tiscalinet.it
SOURCE: JOURNAL OF NEPHROLOGY, (2002 Nov-Dec) 15 Suppl 6 S86-93.
Ref: 54
Journal code: 9012268. ISSN: 1120-3625.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030108
Last Updated on STN: 20030410
Entered Medline: 20030409
AB Chronic renal failure is often complicated by altered calcium and phosphate omeostasis. Many patients develop secondary hyperparathyroidism during the course of the disease. Therefore, both prevention and treatment of secondary hyperparathyroidism are central issues in the treatment of uremic patients. Active ***vitamin*** ***D*** metabolites are important agents in uremic patients, who have a defective activity of the renal 1alpha-hydroxylase responsible for calcitriol synthesis. However, treatment with calcitriol has some limitations, namely an increase in intestinal phosphate absorption, a possible calcium overload and therefore an increase in CaxP ion product. These limitations stimulated an active research on the development of ***vitamin*** ***D*** ***analogs*** with reduced effects on intestinal transport as well as on bone mobilization of calcium and phosphate. Three ***vitamin*** ***D*** ***analogs*** , which have been used in humans, are reviewed in this article: ***22*** - ***oxacalcitriol*** (Maxacalcitol), 19-nor-1alpha,25(OH)2 vitamin D2 (Paricalcitol), and 1alpha(OH) Vitamin D2 (Doxercalciferol). In addition, a new pharmacologic approach to the treatment of secondary hyperparathyroidism has been developed: the use of agonists for the parathyroid calcium sensing receptor, or calcimimetics. AMG O73, a second generation agent, is now under clinical evaluation in phase 3 studies, and it will soon be available in clinical practice. Given the different mechanism of action, it will be possible to use it along with ***vitamin*** ***D*** ***analogs*** and non calcemic phosphate binders. A broader spectrum of therapeutic approaches will enable the nephrologist to individually tailor the treatment of secondary hyperparathyroidism.

L8 ANSWER 7 OF 32 MEDLINE on STN
ACCESSION NUMBER: 2002628907 MEDLINE
DOCUMENT NUMBER: 22274585 PubMed ID: 12386269
TITLE: Effects of i.v. and oral 1,25-dihydroxy-22-oxavitamin D(3) on secondary hyperparathyroidism in dogs with chronic renal failure.
AUTHOR: Takahashi Fumiaki; Furuichi Tatsuya; Yorozu Keigo; Kawata

Setsu; Kitamura Hidetomo; Kubodera Noboru; Slatopolsky Eduardo
CORPORATE SOURCE: Chugai Pharmaceutical Co Ltd, Gotemba, Shizuoka, Japan.. takahashifma@chugai-pharm.co.jp
SOURCE: NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (2002) 17 Suppl 10 46-52.
Journal code: 8706402. ISSN: 0931-0509.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20021019
Last Updated on STN: 20030418
Entered Medline: 20030417

AB BACKGROUND: 1,25-Dihydroxyvitamin D(3) (1,25(OH)(2)D(3), calcitriol) has been used for the treatment of secondary hyperparathyroidism (2HPT) associated with chronic renal failure (CRF). However, hypercalcaemia frequently precludes the administration of ideal doses of 1,25(OH)(2)D(3). 1,25-Dihydroxy-22-oxavitamin D(3) (***22*** - ***oxacalcitriol*** , OCT) is an analogue of 1,25(OH)(2)D(3) with less calcaemic activity. Several investigators have reported the effect of this analogue on suppressing parathyroid hormone (***PTH***) in vitro and in vivo in rats and dogs. METHODS AND RESULTS: The first experiments were designed to compare the relative potency of an i.v. injection of OCT and 1,25(OH)(2)D(3) (i.v. OCT vs i.v. 1,25(OH)(2)D(3)) on serum ***PTH*** and ionized calcium (ICa). A single dose of OCT (5 microg/kg) to uraemic dogs suppressed ***PTH*** by 81% without a statistical significant change in serum ICa. On the other hand, any of the effective doses of 1,25(OH)(2)D(3) on ***PTH*** suppression were hypercalcaemic. The intermittent administration of OCT (0.1 microg/kg) or 1,25(OH)(2)D(3) (0.025 microg/kg), three times per week i.v. suppressed serum ***PTH*** by 89 or 77%, respectively without hypercalcaemia. To evaluate OCT as an oral drug, it was given intermittently (three times per week) to a group of six dogs for a period of 4 weeks. Subsequently, it was changed to a daily administration (0.05 microg/kg) for a period of 2 weeks. Finally the dose was reduced to 0.025 microg/kg. Daily OCT 0.05 microg/kg suppressed serum ***PTH*** by 67%. Subsequently, 0.025 microg/kg maintained serum ***PTH*** within the normal range without hypercalcaemia for 4 weeks. The time course of serum OCT concentrations following a single i.v. or oral OCT dose to uraemic dogs showed that oral OCT was rapidly absorbed and reached maximum plasma concentration and its disappearance from blood was similar to that of i.v. injection. CONCLUSIONS: In conclusion, our results suggest that OCT is a useful ***vitamin*** ***D*** (3) analogue, with a potentially larger therapeutic window than that of i.v. 1,25(OH)(2)D(3) and which is available for i.v./oral, in the management of 2HPT.

L8 ANSWER 8 OF 32 MEDLINE on STN
ACCESSION NUMBER: 2002628906 MEDLINE
DOCUMENT NUMBER: 22274584 PubMed ID: 12386268
TITLE: A comparison between 1,25-dihydroxy-22-oxavitamin D(3) and 1,25-dihydroxyvitamin D(3) regarding suppression of parathyroid hormone secretion and calcaemic action.
AUTHOR: Hirata Michinori; Endo Koichi; Katsumata Kyoko; Ichikawa Fumihiko; Kubodera Noboru; Fukagawa Masafumi
CORPORATE SOURCE: Fuji Gotemba Research Labs, Chugai Pharmaceutical Co, Ltd, Shizuoka, Japan.
SOURCE: NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (2002) 17 Suppl 10 41-5.
Journal code: 8706402. ISSN: 0931-0509.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20021019

Last Updated on STN: 20030418
Entered Medline: 20030417

AB BACKGROUND: Since Slatopolsky et al. (J Clin Invest 1984; 74: 2136-2143) reported the effect of active ***vitamin*** ***D*** , 1,25-dihydroxyvitamin D(3) (1,25(OH)(2)D(3)), on secondary hyperparathyroidism (2HPT) which accompanies chronic renal failure, there have been several studies of the therapeutic effects of 1,25(OH)(2)D(3) in this disease. Although parathyroid hormone (***PTH***) is suppressed by treatment with 1,25(OH)(2)D(3), long-term treatment with 1,25(OH)(2)D(3) tends to induce hypercalcaemia. Therefore, an analogue of 1,25(OH)(2)D(3), 1,25-dihydroxy-22-oxavitamin D(3) (***22*** - ***oxacalcitriol*** , OCT) with less calcaemic activity, was developed for the treatment of 2HPT. METHODS: In order to clarify the differences between the effects of 1,25(OH)(2)D(3) and OCT on 2HPT associated with chronic renal failure, these compounds were administered by intermittent i.v. injection for 2 weeks in rats with mild to moderate uraemia. RESULTS: 1,25(OH)(2)D(3) markedly suppressed ***PTH*** levels, but increased serum calcium (Ca). OCT also markedly suppressed ***PTH*** levels, but induced only a slight increase in serum Ca. 1,25(OH)(2)D(3) caused a dose-dependent decrease in body weight, whereas OCT had no effect on body weight in uraemic rats. Based on those doses of OCT and 1,25(OH)(2)D(3), which resulted in a 60% suppression of ***PTH*** , and induced hypercalcaemia, we consider the relative ratios for efficacy and Ca-elevating activity between OCT and 1,25(OH)(2)D(3) to be 1 : 8 and 1 : 48, respectively. CONCLUSIONS: OCT suppressed ***PTH*** levels with a slight increase in serum Ca without changing the body weight in uraemic rats. This observation suggests that OCT might be a useful ***vitamin*** ***D*** analogue for 2HPT management in long-term clinical treatment.

L8 ANSWER 9 OF 32 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002628905 MEDLINE
DOCUMENT NUMBER: 22274580 PubMed ID: 12386264
TITLE: ***Vitamin*** ***D*** analogues for secondary hyperparathyroidism.
AUTHOR: Brown Alex J; Dusso Adriana S; Slatopolsky Eduardo
CORPORATE SOURCE: Renal Division, Washington University School of Medicine, St Louis, Missouri, USA.. abrown@imgate.wustl.edu
SOURCE: NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (2002) 17 Suppl 10 10-9. Ref: 49
Journal code: 8706402. ISSN: 0931-0509.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20021019
Last Updated on STN: 20030418
Entered Medline: 20030417

AB Secondary hyperparathyroidism (2HPT), a common disorder in patients with chronic renal failure, develops in response to phosphate retention and low serum 1,25-dihydroxyvitamin D(3) (1,25(OH)(2)D(3), calcitriol). Replacement therapy with calcitriol or its precursor 1alpha-hydroxyvitamin D(3) (1alphaOHD(3), alfacalcidol) often produces hypercalcaemia, especially when combined with calcium-based phosphate binders. In addition, these ***vitamin*** ***D*** compounds can aggravate the hyperphosphataemia in these patients. Several ***vitamin*** ***D*** analogues have been developed that retain the direct suppressive action of 1,25(OH)(2)D(3) on the parathyroid glands but have less calcaemic activity, thereby offering a safer and more effective means of controlling 2HPT. 1,25-Dihydroxy-19-norvitamin D(2) (19-norD(2)) and 1alpha-hydroxyvitamin D(2) (1alphaOHD(2)) are available in the US and 1,25-dihydroxy-22-oxavitamin D(3) (***22*** - ***oxacalcitriol*** , OCT) and 1,25-dihydroxy-26,26,26,27,27,27-hexafluorovitamin D(3) (1,25(OH)(2)26,27F6 D(3), falecalcitriol) have been approved for use in

Japan. Animal studies have demonstrated that OCT and 19-norD(2) have a wider therapeutic window for suppression of parathyroid hormone (***PTH***) because of their lower calcaemic and phosphataemic activities. The low calcaemic activity of OCT has been attributed to its rapid clearance, which prevents sustained effects on intestinal calcium absorption and bone resorption, but still allows a prolonged suppression of ***PTH*** gene expression and parathyroid cell growth. The calcaemic activity of 19-norD(2) diminishes with the duration of treatment by as yet unknown mechanisms. The lower toxicity of 1alphaOHD(2), compared with 1alphaOHD(3), has also been noted with chronic, but not acute administration, perhaps due to differential metabolism. The unique actions of falecalcitriol may also result from an altered metabolism. A clear understanding of the molecular basis for the selectivity of ***vitamin*** ***D*** analogues on parathyroid function may allow the design of even more effective analogues.

L8 ANSWER 10 OF 32 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002628904 MEDLINE
DOCUMENT NUMBER: 22274579 PubMed ID: 12386263
TITLE: Use and indication of ***vitamin*** ***D*** and ***vitamin*** ***D*** analogues in patients with renal bone disease.
AUTHOR: Malluche Hartmut H; Monier-Faugere Marie-Claude; Koszewski Nick J
CORPORATE SOURCE: University of Kentucky Medical Center, Division of Nephrology, Bone and Mineral Metabolism, Lexington, Kentucky 40536-0298, USA.. hhmall@uky.edu
CONTRACT NUMBER: DK51530 (NIDDK)
DK54276 (NIDDK)
M01 RR02602 (NCRR)
SOURCE: NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (2002) 17 Suppl 10 6-9. Ref: 18
Journal code: 8706402. ISSN: 0931-0509.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20021019
Last Updated on STN: 20030418
Entered Medline: 20030417

AB ***Vitamin*** ***D*** plays a pivotal role in the pathogenesis and treatment of renal bone disease. ***Vitamin*** ***D*** levels decline in the early phase of renal failure, however, through a compensatory mechanism parathyroid hormone (***PTH***) stimulates the production of 1,25-dihydroxyvitamin D(3) (1,25(OH)(2)D(3), calcitriol) to return it to normal circulating concentrations. Nevertheless, resistance to calcitriol is observed and may be related to the decreased presence of the heterodimeric, DNA-binding partner for the ***vitamin*** ***D*** receptor protein. In end-stage kidney disease (ESKD) the circulating levels of calcitriol are invariably low. The indications of ***vitamin*** ***D*** therapy are the replacement of the missing hormone vs suppression of hyperparathyroidism (HPT) requiring daily low-dose oral vs intermittent 'pulse' or oral administration. However, this therapy must be accompanied by careful patient monitoring to avoid hypercalcaemia and low bone turnover. Low bone turnover is not merely a histologic entity, but a clinical condition associated with a high risk of extraosseous calcifications, in particular in the cardiovascular system, leading to increased morbidity. Thus, determination of bone turnover in patients with ESKD is essential. Bone biopsy is the gold standard to assess bone turnover, however, it is not always available and nephrologists rely on ***PTH*** levels. The intact ***PTH*** assay measures ***PTH*** (1-84) and large C- ***PTH*** fragments, which may antagonize the ***PTH*** (1-84) effects on bone. An assay that measures exclusively ***PTH*** (1-84) has recently become

available and a calculated ***PTH*** (1-84)/C- ***PTH*** fragment ratio has been shown to be the best predictor of bone turnover in patients with ESKD not treated with ***vitamin*** ***D*** or with other medications known to affect bone metabolism. 1,25-dihydroxy-22-oxavitamin D(3) (***22*** - ***oxacalcitriol*** , OCT) is a ***vitamin*** ***D*** analogue that could control serum ***PTH*** concentrations without deleterious effects on bone.

L8 ANSWER 11 OF 32 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002086912 EMBASE
TITLE: Strategies to minimize bone disease in renal failure.
AUTHOR: Martin K.J.; Gonzalez E.A.
CORPORATE SOURCE: K.J. Martin, Division of Nephrology (9-FDT), 3635 Vista, St. Louis, MO 63110, United States. martinkj@slu.edu
SOURCE: American Journal of Kidney Diseases, (2001) 38/6 (1430-1436).
Refs: 46
ISSN: 0272-6386 CODEN: AJKDDP
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 003 Endocrinology
028 Urology and Nephrology
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The skeletal disorders associated with renal insufficiency result from alterations in calcium, phosphorus, and ***vitamin*** ***D*** metabolism. Each requires intervention to prevent and control the problem. Hyperparathyroidism and its treatment can also result in extraskeletal complications. To prevent the development of parathyroid hyperplasia and the skeletal complications of chronic kidney disease, it is desirable to initiate interventions early in the course of kidney disease; however, many patients present with established hyperparathyroidism and additional strategies are necessary to suppress hyperparathyroidism. Mainstays of this approach are the control of phosphorus and the use of ***vitamin*** ***D*** ***analogs*** . Phosphorus control requires the use of phosphate binders, preferably non-calcium-containing binders, to prevent intestinal phosphorus absorption. ***Vitamin*** ***D*** ***analogs*** are used to suppress hyperparathyroidism and have the potential to have lesser toxicity than calcitriol. Paricalcitol is the most widely used ***vitamin*** ***D*** analog in this country and it effectively suppresses hyperparathyroidism with only minimal effects on calcium and phosphorus. A substantial body of data in experimental animals supports the use of paricalcitol as a preferential therapeutic agent. Recently, an additional ***vitamin*** ***D*** sterol, doxercalciferol, has been introduced, which is metabolized to 1,25-dihydroxyvitamin D(2). Although initially thought to have lesser toxicity than its ***vitamin*** ***D*** (3) counterpart, recent studies have not provided support for a major difference in this regard. Doxercalciferol is also effective in lowering parathyroid hormone (***PTH***), though hypercalcemia in hyperphosphatemic episodes occurred relatively frequently during the clinical studies. As these therapeutic strategies are undertaken, it is important not to oversuppress ***PTH*** and decrease bone turnover to abnormally low levels because of the risk for adynamic retial bone disease. It is possible that when bone turnover is abnormally low, the extraskeletal deposition of calcium in blood vessels and other tissues is enhanced. Accordingly, constant monitoring is required during treatment, with emphasis on minimizing the calcium load, and, if monitored correctly, a satisfactory control of hyperparathyroidism may be achieved with the agents currently available. .COPYRGT. 2001 by the National Kidney Foundation, Inc.

L8 ANSWER 12 OF 32 MEDLINE on STN
ACCESSION NUMBER: 2001529989 MEDLINE

DOCUMENT NUMBER: 21460170 PubMed ID: 11576942
TITLE: Clinical effects of maxacalcitol on secondary hyperparathyroidism of uremic patients.
AUTHOR: Akizawa T; Suzuki M; Akiba T; Nishizawa Y; Kurokawa K
CORPORATE SOURCE: Center of Blood Purification Therapy, Wakayama Medical University, Wakayama.. akizawa@wakayama-med.ac.jp
SOURCE: AMERICAN JOURNAL OF KIDNEY DISEASES, (2001 Oct) 38 (4 Suppl 1) S147-51.
Journal code: 8110075. ISSN: 1523-6838.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011001
Last Updated on STN: 20030313
Entered Medline: 20011204
AB Maxacalcitol (***22*** - ***oxacalcitriol*** [OCT]) is a newly developed ***vitamin*** ***D*** analogue in Japan. OCT has shown less calcemic action and a strong suppressive effect on parathyroid hormone (***PTH***) in uremic rats and dogs. In uremic patients with secondary hyperparathyroidism, OCT dose-dependently suppressed ***PTH*** secretion and increased serum calcium levels. However, more than 60% of patients achieved a greater than 30% decrease in intact ***PTH*** level from baseline with long-term OCT treatment up to 1 year without an unphysiological increase in mean serum calcium levels. Long-term treatment also brought about a reduction in bone metabolic markers, including bone alkaline phosphatase, tartrate-resistant acid phosphatase, and bone gra-protein. These results suggest that although careful attention should be paid to the onset of hypercalcemia and oversuppression of ***PTH*** , OCT is one of the effective tools for the treatment of secondary hyperparathyroidism.

L8 ANSWER 13 OF 32 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2001020564 EMBASE
TITLE: Control of secondary hyperparathyroidism by ***vitamin*** ***D*** derivatives.
AUTHOR: Drueke T.B.
CORPORATE SOURCE: Dr. T.B. Drueke, Inserm Unit 705, Hopital Necker, 161 rue de Sevres, 75743 Paris Cedex 15, France. drueke@necker.fr
SOURCE: American Journal of Kidney Diseases, (2001) 37/1 SUPPL. 2 (S58-S61).
Refs: 20
ISSN: 0272-6386 CODEN: AJKDDP
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 003 Endocrinology
028 Urology and Nephrology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The treatment of the secondary hyperparathyroidism of chronic renal failure patients has greatly improved during the last 2 decades. Significant progress has been made, in particular in the indication of 1.alpha.-hydroxylated ***vitamin*** ***D*** derivatives and patient management using these compounds. Treatment and prevention should start early during the development of chronic renal insufficiency. One of the major remaining problems in more advanced stages of renal failure is that control of plasma phosphate often remains extremely difficult. New inert oral phosphate binders are needed. The nephrology community is still waiting for the advent of nonhypercalcemic and nonhyperphosphatemic ***vitamin*** ***D*** ***analogs*** with ***PTH*** suppressive activity equal to the parent compound calcitriol or its immediate precursor, alfacalcidol. .COPYRGT. 2001 by the National Kidney Foundation, Inc.

L8 ANSWER 14 OF 32 MEDLINE on STN
ACCESSION NUMBER: 2001122402 MEDLINE
DOCUMENT NUMBER: 20549202 PubMed ID: 11096138
TITLE: Potent suppression of the parathyroid glands by hydroxylated metabolites of dihydrotachysterol(2).
AUTHOR: Fan S L; Schroeder N J; Calverley M J; Burrin J M; Makin H L; Cunningham J
CORPORATE SOURCE: Department of Nephrology, St Bartholomew's and the Royal London School of Medicine and Dentistry, London, UK.
SOURCE: NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (2000 Dec) 15 (12) 1943-9.
Journal code: 8706402. ISSN: 0931-0509.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20030313
Entered Medline: 20010222
AB BACKGROUND: Dihydrotachysterol(2), a licensed pharmaceutical, is hydroxylated to 25-hydroxydihydrotachysterol(2) (25(OH)DHT(2)) and 1 alpha,25-dihydroxydihydrotachysterol(2) (1 alpha,25(OH)(2)DHT(2)) in man. We have compared the biological activity of these metabolites with calcitriol and the 'non-calcaemic' analogue, ***22*** - ***oxacalcitriol*** (OCT) in bovine parathyroid cell cultures and in rats. METHODS: The effect of each sterol on parathyroid hormone (***PTH***) secreted by primary bovine parathyroid cells was measured. High-performance liquid chromotography and gas chromotography-mass spectrometry were used to investigate in vitro 25(OH)DHT(2) metabolism. Rats were given a single intraperitoneal injection or five daily injections of each sterol, and changes in ionized calcium and ***PTH*** were measured. RESULTS: In vitro, all sterols suppressed ***PTH*** significantly. Calcitriol and OCT were of similar potency, but 1 alpha, 25(OH)(2)DHT(2) and 25(OH)DHT(2) required higher concentrations to suppress ***PTH*** equally. We were unable to detect metabolism of 25(OH)DHT(2) to 1 alpha,25(OH)(2)DHT(2) in vitro. In rats, a single dose of 0.5 microg/rat of calcitriol increased ionized calcium at 30 and 40 h (statistically significant at 48 h). 50 microg of OCT and 1 alpha,25(OH)(2)DHT(2) did not cause significant hypercalcaemia at 48 h, although 1 alpha,25(OH)(2)DHT(2) caused hypercalcaemia at 30 h. In contrast, 50 microg of 25(OH)DHT(2) caused hypercalcaemia at 48 h but not at 30 h. Five daily doses of 0.001 microg/rat of calcitriol caused a significant rise in calcium and a 50% fall in ***PTH*** . OCT and 1 alpha,25(OH)(2)DHT(2) at 0.025 and 0.5 microg/rat respectively caused similar suppression of ***PTH*** but without hypercalcaemia. CONCLUSION: 1 alpha,25(OH)(2)DHT(2) and 25(OH)DHT(2) are potent suppressors of ***PTH*** in vitro and in vivo. 25(OH)DHT(2) may be active by virtue of its pseudo-1 alpha-hydroxyl group. Hypercalcaemia caused by a single dose of 1 alpha,25(OH)(2)DHT(2) appeared to be more transient than calcitriol. Five daily doses of 1 alpha, 25(OH)(2)DHT(2) and OCT could achieve 50% suppression of ***PTH*** without significant increments in ionized calcium. In contrast, suppression of ***PTH*** by calcitriol was associated with significant increments in ionized calcium. These data suggest that like OCT, 1 alpha, 25(OH)(2)DHT(2) can dissociate calcaemic actions from parathyroid-suppressing actions in a manner that may be therapeutically useful.

L8 ANSWER 15 OF 32 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:309455 CAPLUS
DOCUMENT NUMBER: 133:275780
TITLE: ***Vitamin*** ***D*** therapy in renal osteodystrophy
AUTHOR(S): Tsukamoto, Yusuke
CORPORATE SOURCE: Adult Disease Res. Lab., Morishita Memorial Hosp., Japan

SOURCE: Bone (Osaka) (2000), 14(2), 233-238
CODEN: BONEFN; ISSN: 0914-7047
PUBLISHER: Medikaru Rebyusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 25 refs. The historical changes in therapy on bone anomaly in hemodialysis is described including active ***vitamin*** ***D*** (AVD) therapy. Recently developed AVD i.v. pulse therapy is discussed including Japanese situation, which uses calcitriol and ***22*** - ***oxacalcitriol*** . Other AVD ***analogs*** under development are described; 24,25-dihydroxy D3, 26,27-hexafluoro-1,25-dihydroxy D3 and 19-nor-10-oxo-25-hydroxy D3. The administration of AVD in clin. situation is discussed including parathyroid hormone (***PTH***) level and using AVD species. The diagnosis of renal osteodystrophy is schematically depicted, and the author considers that intermittent administration of AVD is necessary in the case ***PTH*** <65 pg/mL in osteodystrophy.

L8 ANSWER 16 OF 32 MEDLINE on STN
ACCESSION NUMBER: 2000111596 MEDLINE
DOCUMENT NUMBER: 20111596 PubMed ID: 10646127
TITLE: 1,25-dihydroxyvitamin D3 as well as its analogue OCT lower blood calcium through inhibition of bone resorption in hypercalcemic rats with continuous parathyroid hormone-related peptide infusion.
AUTHOR: Endo K; Katsumata K; Hirata M; Masaki T; Kubodera N; Nakamura T; Ikeda K; Ogata E
CORPORATE SOURCE: Pharmaceutical Research Laboratory, Chugai Pharmaceutical Co. Ltd., Tokyo, Japan.
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (2000 Jan) 15 (1) 175-81.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20030313
Entered Medline: 20000211

AB The effects of 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] and its analogue 22-oxa-1,25(OH)2D3 (***22*** - ***oxacalcitriol***) (OCT) on calcium and bone metabolism were examined in an animal model of hypercalcemia with continuous infusion of parathyroid hormone-related peptide (PTHrP), to determine whether active ***vitamin*** ***D*** could counteract the skeletal action of PTHrP in addition to its reported effect in suppressing the production of PTHrP in cancer cells. Parathyroid glands were removed from 8-week-old Sprague-Dawley rats to eliminate the confounding effects of endogenous ***PTH*** . Animals were then continuously infused with human PTHrP(1-34) at a constant rate via osmotic minipumps for 2 weeks, and at the same time treated orally or intravenously with OCT or 1,25(OH)2D3 four to nine times during the 2-week period. Under these conditions, OCT and, surprisingly, 1,25(OH)2D3 alleviated hypercalcemia in a dose-dependent manner. 1,25(OH)2D3 and OCT suppressed the urinary excretion of deoxypyridinoline, although they did not affect renal calcium handling, suggesting that the antihypercalcemic effect is attributable to the inhibition of bone resorption. These active ***vitamin*** ***D*** compounds also counteracted the effects of PTHrP at the proximal renal tubules, as reflected by a decrease in phosphate excretion. Histomorphometric analysis of bone revealed a dose-related decrease in parameters of bone resorption. These results suggest that 1,25(OH)2D3 as well as OCT has the potential to alleviate hypercalcemia, at least in part, through the inhibition of bone resorption in hypercalcemic rats with constant PTHrP levels. We propose that the main function of active ***vitamin*** ***D*** in high bone-turnover states is to inhibit bone resorption, and this may have important implications for the understanding of the role of active ***vitamin*** ***D*** in the treatment of metabolic bone diseases,

such as osteoporosis.

L8 ANSWER 17 OF 32 MEDLINE on STN
ACCESSION NUMBER: 2000063091 MEDLINE
DOCUMENT NUMBER: 20063091 PubMed ID: 10594779
TITLE: ***22*** - ***Oxacalcitriol*** ameliorates high-turnover bone and marked osteitis fibrosa in rats with slowly progressive nephritis.
AUTHOR: Hirata M; Katsumata K; Masaki T; Koike N; Endo K; Tsunemi K; Ohkawa H; Kurokawa K; Fukagawa M
CORPORATE SOURCE: Fuji Gotemba Research Laboratory, Chugai Pharmaceutical Co., Ltd., Shizuoka, Japan.
SOURCE: KIDNEY INTERNATIONAL, (1999 Dec) 56 (6) 2040-7.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000131
Last Updated on STN: 20030313
Entered Medline: 20000114
AB ***22*** - ***Oxacalcitriol*** ameliorates high-turnover bone and marked osteitis fibrosa in rats with slowly progressive nephritis. BACKGROUND: ***22*** - ***Oxacalcitriol*** (OCT) is a unique ***vitamin*** ***D*** analogue with less calcemic activity than calcitriol, and it effectively suppresses parathyroid hormone (***PTH***) secretion in uremic rats. This study was performed to examine the long-term effect of intravenously administered OCT on high-turnover bone disease in model rats of slowly progressive renal failure. METHODS: Slowly progressive renal failure rats were made by a single injection of glycopeptide isolated from rat renal cortical tissues. At 250 days, glycopeptide-induced nephritis (GN) rats were divided into three groups with the same levels of serum creatinine and ***PTH*** , and they received either OCT (0.03 or 0.15 microg/kg body wt) or vehicle given intravenously three times per week for 15 weeks. RESULTS: Renal function of GN rats deteriorated very slowly but progressively, as assessed by the increase of serum creatinine concentration. At sacrifice, serum ***PTH*** levels, bone formation markers, bone resorption markers, and fibrosis volume were significantly elevated in vehicle-treated GN rats compared with those of sham-operated rats, suggesting the development of high-turnover bone disease with osteitis fibrosa. In contrast, in the GN-OCT 0.15 microg/kg group, these high ***PTH*** levels and high-turnover bone and fibrosis were significantly decreased. Such amelioration of bone abnormalities by OCT was not accompanied by either hypercalcemia or further deterioration of renal function. CONCLUSIONS: These data indicate that OCT may be a useful and safe agent not only for the suppression of ***PTH*** , but also for the amelioration of osteitis fibrosa and high-turnover bone without causing hypercalcemia in chronic dialysis patients.

L8 ANSWER 18 OF 32 MEDLINE on STN
ACCESSION NUMBER: 1999152205 MEDLINE
DOCUMENT NUMBER: 99152205 PubMed ID: 10027919
TITLE: ***22*** - ***oxacalcitriol*** suppresses secondary hyperparathyroidism without inducing low bone turnover in dogs with renal failure.
AUTHOR: Monier-Faugere M C; Geng Z; Friedler R M; Qi Q; Kubodera N; Slatopolsky E; Malluche H H
CORPORATE SOURCE: Division of Nephrology, Bone and Mineral Metabolism, Department of Internal Medicine, University of Kentucky, Lexington 40536-0084, USA.
SOURCE: KIDNEY INTERNATIONAL, (1999 Mar) 55 (3) 821-32.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990504
Last Updated on STN: 20030313
Entered Medline: 19990416

AB BACKGROUND: Calcitriol therapy suppresses serum levels of parathyroid hormone (***PTH***) in patients with renal failure but has several drawbacks, including hypercalcemia and/or marked suppression of bone turnover, which may lead to adynamic bone disease. A new ***vitamin*** ***D*** analogue, ***22*** - ***oxacalcitriol*** (OCT), has been shown to have promising characteristics. This study was undertaken to determine the effects of OCT on serum ***PTH*** levels and bone turnover in states of normal or impaired renal function. METHODS: Sixty dogs were either nephrectomized (Nx, N = 38) or sham-operated (Sham, N = 22). The animals received supplemental phosphate to enhance ***PTH*** secretion. Fourteen weeks after the start of phosphate supplementation, half of the Nx and Sham dogs received doses of OCT (three times per week); the other half were given vehicle for 60 weeks. Thereafter, the treatment modalities for a subset of animals were crossed over for an additional eight months. Biochemical and hormonal indices of calcium and bone metabolism were measured throughout the study, and bone biopsies were done at baseline, 60 weeks after OCT or vehicle treatment, and at the end of the crossover period. RESULTS: In Nx dogs, OCT significantly decreased serum ***PTH*** levels soon after the induction of renal insufficiency. In long-standing secondary hyperparathyroidism, OCT (0.03 microg/kg) stabilized serum ***PTH*** levels during the first months. Serum ***PTH*** levels rose thereafter, but the rise was less pronounced compared with baseline than the rise seen in Nx control. These effects were accompanied by episodes of hypercalcemia and hyperphosphatemia. In animals with normal renal function, OCT induced a transient decrease in serum ***PTH*** levels at a dose of 0.1 microg/kg, which was not sustained with lowering of the doses. In Nx dogs, OCT reversed abnormal bone formation, such as woven osteoid and fibrosis, but did not significantly alter the level of bone turnover. In addition, OCT improved mineralization lag time, (that is, the rate at which osteoid mineralizes) in both Nx and Sham dogs. CONCLUSIONS: These results indicate that even though OCT does not completely prevent the occurrence of hypercalcemia in experimental dogs with renal insufficiency, it may be of use in the management of secondary hyperparathyroidism because it does not induce low bone turnover and, therefore, does not increase the risk of adynamic bone disease.

L8 ANSWER 19 OF 32 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1999141547 MEDLINE
DOCUMENT NUMBER: 99141547 PubMed ID: 9987074
TITLE: Effects of new analogues of ***vitamin*** ***D*** on bone cells: implications for treatment of uremic bone disease.
AUTHOR: McIntyre C W; Schroeder N J; Burrin J M; Cunningham J
CORPORATE SOURCE: Department of Renal Medicine and Transplantation, Royal London Hospital, United Kingdom.
SOURCE: KIDNEY INTERNATIONAL, (1999 Feb) 55 (2) 500-11.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 20030313
Entered Medline: 19990415

AB BACKGROUND: The use of calcitriol in the treatment of uremic hyperparathyroidism and renal osteodystrophy is limited in many patients by hypercalcemic side-effects. New less calcemic analogues of calcitriol are being developed, and some are under clinical evaluation. To investigate whether these compounds possess important differences in their action on bone cells, we have studied their effects [with and without

parathyroid hormone (***PTH***)] on the release and synthesis of the resorptive osteotropic cytokine, interleukin-6 (IL-6). METHODS: MG 63 and SaOS-2 human osteoblastic cell lines were cultured for 6 or 24 hours in media containing calcitriol, the sterols of interest, or 1-34 synthetic ***PTH*** . IL-6 release was assayed by commercially available enzyme-linked immunosorbent assay. IL-6 mRNA levels were assessed by reverse transcriptase-polymerase chain reaction. RESULTS: We found that calcitriol and paricalcitol behaved in a similar fashion, resulting in increased IL-6 release only at higher concentrations (10(-7) to 10(-9) M). In contrast, ***22*** - ***oxacalcitriol*** and 1,25-dihydroxydihydrotachysterol2 stimulated release to a similar extent but at concentrations three to four orders of magnitude lower (10(-11) to 10(-13) M), despite being less potent as suppressers of parathyroid function than calcitriol. Studies of IL-6 mRNA showed a similar pattern of concentration and cell line-dependent transcription. CONCLUSIONS: Compounds stimulating IL-6 release at concentrations achievable during the treatment of uremic hyperparathyroidism might favor continuing linked bone formation and resorption and thereby avoid adynamic bone disease while still allowing profound suppression of ***PTH*** .

L8 ANSWER 20 OF 32 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2000149017 MEDLINE
DOCUMENT NUMBER: 20149017 PubMed ID: 10681662
TITLE: ***Vitamin*** ***D*** ***analogs*** : perspectives for treatment.
AUTHOR: Brown A J; Slatopolsky E
CORPORATE SOURCE: Renal Division, Washington University School of Medicine, St. Louis, MO 63110, USA.. abrown@imgate.wustl.edu
CONTRACT NUMBER: DK09976 (NIDDK)
SOURCE: MINERAL AND ELECTROLYTE METABOLISM, (1999 Jul-Dec) 25 (4-6) 337-41. Ref: 18
Journal code: 7802196. ISSN: 0378-0392.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000427
Last Updated on STN: 20030313
Entered Medline: 20000420
AB ***Vitamin*** ***D*** therapy is widely used for the treatment of secondary hyperparathyroidism associated with chronic renal failure. However, administration of 1,25-dihydroxyvitamin D(3) [1,25(OH)(2)D(3)] or its precursor 1alpha(OH)D(3), especially in combination with calcium-based phosphate binders, often produces hypercalcemia. Several ***vitamin*** ***D*** ***analogs*** have been developed that retain the direct suppressive action of 1,25(OH)(2)D(3) on the parathyroid glands but have less calcemic activity. These ***analogs*** offer a safer and more effective means of controlling secondary hyperparathyroidism. 22-Oxa-1,25(OH)(2)D(3) (***22*** - ***oxacalcitriol*** or OCT), 19-nor-1, 25(OH)(2)D(2) (19-norD(2)) and 1alpha(OH)D(2) have been tested in animal models of uremia and in clinical trials. Intravenous 19-norD(2) and oral 1alpha(OH)D(2) have been approved for use in the United States; OCT is currently under review. The mechanisms by which these ***analogs*** exert their selective actions on the parathyroid glands are under investigation. The low calcemic activity of OCT has been attributed to its rapid clearance which prevents sustained effects on intestinal calcium absorption and bone resorption, but still allows a prolonged suppression of ***PTH*** gene expression. The selectivity of 19-norD(2) and 1alpha(OH)D(2) is achieved by a distinct mechanism(s). Knowledge of how these compounds exert their selective actions on the parathyroid glands may allow the design of more effective ***analogs*** in the future.

L8 ANSWER 21 OF 32 MEDLINE on STN DUPLICATE 6

ACCESSION NUMBER: 2000099281 MEDLINE
DOCUMENT NUMBER: 20099281 PubMed ID: 10633464
TITLE: New ***analogs*** of vitamin D3.
AUTHOR: Slatopolsky E; Dusso A; Brown A
CORPORATE SOURCE: Renal Division, Washington University School of Medicine, St. Louis, Missouri, USA.
SOURCE: KIDNEY INTERNATIONAL. SUPPLEMENT, (1999 Dec) 73 S46-51.
Ref: 27
Journal code: 7508622. ISSN: 0098-6577.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000209
Last Updated on STN: 20000309
Entered Medline: 20000128

AB Calcitriol, the most active metabolite of ***vitamin*** ***D*** , controls parathyroid gland growth and suppresses the synthesis and secretion of parathyroid hormone (***PTH***). However, because of its potent effects on intestinal calcium absorption and bone mobilization, calcitriol treatment can induce hypercalcemia, often precluding its use at therapeutic doses. Hyperphosphatemia is also a persistent problem among patients undergoing chronic hemodialysis and can be aggravated by therapeutic doses of calcitriol. Several pharmaceutical companies were able to modify the side-chain of the 1,25(OH)2D3, allowing some of these new ***analogs*** to retain the action on the parathyroid glands while decreasing their hypercalcemic and hyperphosphatemic effects. The structure-activity relationship for ligand-mediated transcriptional regulation has been studied in detail. In some ***analogs*** the serum binding protein (DBP) plays a key role in determining the pharmacokinetics of the ***vitamin*** ***D*** compound. The affinity to DBP for ***22*** - ***oxacalcitriol*** (OCT), an analog of calcitriol for the treatment of secondary hyperparathryoidism, is approximately 300-400 times lower than that of calcitriol and the analog is rapidly cleared from the circulation. The mechanisms for the selectivity of 19-nor-1,25(OH)2D2 (paricalcitol) (Zemplar) another analog of calcitriol, is clearly different from OCT. Although the mechanisms of action is not completely known, it does appear that paricalcitol down-regulates the VDR in the intestine. It is likely that the unique biological profiles of ***vitamin*** ***D*** ***analogs*** in vivo are due to multiple mechanisms. Understanding the molecular basis of the analog selectivity will not only provide an explanation for their unique actions but allow intelligent design of more effective ***analogs*** in the future.

L8 ANSWER 22 OF 32 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000009025 EMBASE
TITLE: New ***analogs*** of vitamin D3.
AUTHOR: Slatopolsky E.; Dusso A.; Brown A.
CORPORATE SOURCE: Dr. E. Slatopolsky, Washington Univ. School of Medicine, Renal Division, 660 South Euclid Ave., St. Louis, MO 63110, United States
SOURCE: Kidney International, Supplement, (1999) 56/73 (S46-S51).
Refs: 27
ISSN: 0098-6577 CODEN: KISUDF
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

SUMMARY LANGUAGE: English

AB Calcitriol, the most active metabolite of ***vitamin*** ***D*** , controls parathyroid gland growth and suppresses the synthesis and secretion of parathyroid hormone (***PTH***). However, because of its potent effects on intestinal calcium absorption and bone mobilization, calcitriol treatment can induce hypercalcemia, often precluding its use at therapeutic doses. Hyperphosphatemia is also a persistent problem among patients undergoing chronic hemodialysis and can be aggravated by therapeutic doses of calcitriol. Several pharmaceutical companies were able to modify the side- chain of the 1,25(OH)2D3, allowing some of these new ***analogs*** to retain the action on the parathyroid glands while decreasing their hypercalcemic and hyperphosphatemic effects. The structure-activity relationship for ligand- mediated transcriptional regulation has been studied in detail. In some ***analogs*** the serum binding protein (DBP) plays a key role in determining the pharmacokinetics of the ***vitamin*** ***D*** compound. The affinity to DBP for ***22*** - ***oxacalcitriol*** (OCT), an analog of calcitriol for the treatment of secondary hyperparathyroidism, is approximately 300-400 times lower than that of calcitriol and the analog is rapidly cleared from the circulation. The mechanisms for the selectivity of 19-nor-1,25(OH)2D2 (paricalcitol) (Zemplar.RTM.) another analog of calcitriol, is clearly different from OCT. Although the mechanisms of action is not completely known, it does appear that paricalcitol down-regulates the VDR in the intestine. It is likely that the unique biological profiles of ***vitamin*** ***D*** ***analogs*** in vivo are due to multiple mechanisms. Understanding the molecular basis of the analog selectivity will not only provide an explanation for their unique actions but allow intelligent design of more effective ***analogs*** in the future.

L8 ANSWER 23 OF 32 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:80604 BIOSIS
DOCUMENT NUMBER: PREV200000080604
TITLE: New ***analogs*** of vitamin D3.
AUTHOR(S): Slatopolsky, Eduardo (1); Dusso, Adriana; Brown, Alex
CORPORATE SOURCE: (1) Renal Division, Washington University School of Medicine, 660 South Euclid Ave., Saint Louis, MO USA
SOURCE: Kidney International Supplement, (Dec., 1999) Vol. 0, No. 73, pp. S.46-S.51.
ISSN: 0098-6577.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Calcitriol, the most active metabolite of ***vitamin*** ***D*** , controls parathyroid gland growth and suppresses the synthesis and secretion of parathyroid hormone (***PTH***). However, because of its potent effects on intestinal calcium absorption and bone mobilization, calcitriol treatment can induce hypercalcemia, often precluding its use at therapeutic doses. Hyperphosphatemia is also a persistent problem among patients undergoing chronic hemodialysis and can be aggravated by therapeutic doses of calcitriol. Several pharmaceutical companies were able to modify the side-chain of the 1,25(OH)2D3, allowing some of these new ***analogs*** to retain the action on the parathyroid glands while decreasing their hypercalcemic and hyperphosphatemic effects. The structure-activity relationship for ligand-mediated transcriptional regulation has been studied in detail. In some ***analogs*** the serum binding protein (DBP) plays a key role in determining the pharmacokinetics of the ***vitamin*** ***D*** compound. The affinity to DBP for ***22*** - ***oxacalcitriol*** (OCT), an analog of calcitriol for the treatment of secondary hyperparathryoidism, is approximately 300-400 times lower than that of calcitriol and the analog is rapidly cleared from the circulation. The mechanisms for the selectivity of 19-nor-1,25(OH)2D2 (paricalcitol) (Zemplar(R)) another analog of calcitriol, is clearly different from OCT. Although the mechanisms of action is not completely known, it does appear that paricalcitol down-regulates the VDR in the intestine. It is likely that the unique biological profiles of ***vitamin*** ***D*** ***analogs*** in vivo are due to multiple mechanisms. Understanding the molecular basis of the analog selectivity

will not only provide an explanation for their unique actions but allow intelligent design of more effective ***analogs*** in the future.

L8 ANSWER 24 OF 32 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1998151001 MEDLINE
DOCUMENT NUMBER: 98151001 PubMed ID: 9492037
TITLE: The noncalcemic ***vitamin*** ***D*** ***analogs*** EB1089 and ***22*** - ***oxacalcitriol*** suppress serum-induced parathyroid hormone-related peptide gene expression in a lung cancer cell line.
AUTHOR: Falzon M; Zong J
CORPORATE SOURCE: Department of Pharmacology and Toxicology and Sealy Center for Molecular Science, University of Texas Medical Branch, Galveston 77555, USA.. mfalzon@utmb.edu
SOURCE: ENDOCRINOLOGY, (1998 Mar) 139 (3) 1046-53.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980319
Last Updated on STN: 20030313
Entered Medline: 19980312
AB ***PTH*** -related peptide (PTHrP) mediates the syndrome of humoral hypercalcemia of malignancy, a frequent complication of squamous cell carcinomas of the lung. This study was undertaken to determine whether 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] and two nonhypercalcemic ***analogs*** , EB1089 and 22-oxa-1,25-(OH)2D3 (***22*** - ***oxacalcitriol***), suppress serum- and epidermal growth factor (EGF)-induced PTHrP gene expression in a human lung squamous cancer cell line, NCI H520. PTHrP expression was up-regulated by serum and EGF in a concentration- and time-dependent manner. Nuclear run-on analysis showed that this induction was mediated via a transcriptional mechanism, and that sequences within promoter 1 were responsible. All three vitamin D3 compounds decreased both basal and serum- and EGF-induced steady state PTHrP messenger RNA and secreted peptide levels. These effects were again mediated via a transcriptional mechanism through sequences within promoter 1. All three vitamin D3 compounds also decreased the proliferation of NCI H520 cells in a concentration- and time-dependent manner. 1,25-(OH)2D3 is hypercalcemic in vivo. However, the noncalcemic ***analogs*** EB1089 and 22-oxa-1,25-(OH)2D3 have therapeutic potential, as they suppress not only the basal but also the growth factor-stimulated levels of PTHrP in a cancer cell line associated with hypercalcemia.

L8 ANSWER 25 OF 32 MEDLINE on STN
ACCESSION NUMBER: 96437717 MEDLINE
DOCUMENT NUMBER: 96437717 PubMed ID: 8840326
TITLE: Effect of ***22*** - ***oxacalcitriol*** on hyperparathyroidism of dialysis patients: results of a preliminary study.
AUTHOR: Kurokawa K; Akizawa T; Suzuki M; Akiba T; Ogata E; Slatopolsky E
CORPORATE SOURCE: Department of Medicine, University of Tokyo, Japan.
SOURCE: NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (1996) 11 Suppl 3 121-4.
Journal code: 8706402. ISSN: 0931-0509.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20030313
Entered Medline: 19961212
AB Intermittent high dose administration of calcitriol or alfacalcidol is

effective in suppressing secondary hyperparathyroidism in chronic dialysis patients, however calcaemic action of these ***vitamin*** ***D*** derivatives is a major obstacle. ***22*** - ***Oxacalcitriol*** (OCT) has been reported to have less calcaemic action than calcitriol, while preserving a comparable suppressive effect on parathyroid hormone (***PTH***) secretion. This preliminary study was conducted to examine the effects of OCT on secondary hyperparathyroidism in chronic dialysis patients. OCT was administrated intravenously immediately after every haemodialysis session three times a week for 12 weeks to three haemodialysis patients with secondary hyperparathyroidism. An initial dose of OCT of 5.5 micrograms/haemodialysis session was increased stepwise by 5.5 micrograms/haemodialysis up to 22 micrograms/haemodialysis according to the suppression of ***PTH*** and calcaemic action. OCT was discontinued for at least a week when serum calcium adjusted to albumin concentration measured just before haemodialysis exceeded 11.5 mg/dl. Marked reduction in plasma ***PTH*** , alkaline phosphatase and tartrate-resistant acid phosphatase was observed in all three patients. Although the dose of OCT was increased to 22 micrograms/haemodialysis in one patient, the final dose of OCT remained 5.5 micrograms/haemodialysis in the other two patients because of hypercalcaemia. It is concluded that OCT is highly effective in suppressing ***PTH*** in dialysis patients with secondary hyperparathyroidism. Hypercalcaemia may be a major factor which limits the use of OCT, though it may occur with higher doses of OCT than those of calcitriol usually given to suppress ***PTH*** hypersecretion.

L8 ANSWER 26 OF 32 MEDLINE on STN
ACCESSION NUMBER: 96055182 MEDLINE
DOCUMENT NUMBER: 96055182 PubMed ID: 8541145
TITLE: ***22*** - ***Oxacalcitriol*** does not interfere with parathyroid hormone-induced phosphaturia or cyclic-AMP excretion.
AUTHOR: Friedlaender M M; Yagil Y; Wald H; Popovtzer M M
CORPORATE SOURCE: Nephrology Service, Hadassah University Hospital, Jerusalem, Israel.
SOURCE: BONE, (1995 Sep) 17 (3) 301-6.
Journal code: 8504048. ISSN: 8756-3282.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960227
Last Updated on STN: 20030313
Entered Medline: 19960212

AB The ***vitamin*** ***D*** analogue, ***22*** - ***oxacalcitriol*** [22-oxa-1,25(OH)2 vitamin D3], has pleiotropic effects similar to or greater than calcitriol but has markedly fewer calcemic and phosphatemic effects. To test the hypothesis that the lesser phosphatemic effect of ***22*** - ***oxacalcitriol*** is due, at least in part, to a lack of interference with the phosphaturic effect of parathyroid hormone, acute clearance experiments were performed in parathyroidectomized rats receiving continuous 1-34 parathyroid hormone (***PTH***) infusion together with ***22*** - ***oxacalcitriol*** (200 pmol.100 g body weight-1.min-1) or vehicle. In contrast to the previously reported inhibitory effect of calcitriol on ***PTH*** -induced phosphaturia, fractional excretion of phosphorus increased similarly in both groups, from 0.05 +/- 0.01 to 0.26 +/- 0.02 ($p < 0.01$) in the vehicle-infused animals and from 0.04 +/- 0.01 to 0.24 +/- 0.02 ($p < 0.01$) in the ***22*** - ***oxacalcitriol*** -treated rats (p between groups not significant [n.s.]). Urinary cyclic AMP excretion also increased similarly, from 45.5 +/- 5.2 to 101.6 +/- 21.6 ($p < 0.01$) and from 45.4 +/- 5.6 to 102.6 +/- 16.7 pmol/min ($p < 0.01$), respectively (p between groups n.s.). In search for a nongenomic mechanism that might account for the disparate effects of ***22*** - ***oxacalcitriol*** and calcitriol, OK cells, which are reminiscent of the mammalian proximal tubule cell, were stimulated with calcitriol and ***22*** -

oxacalcitriol and free intracellular calcium concentration was determined. At high concentrations, calcitriol caused a dose-dependent increase in [Ca2+]i; ***22*** - ***oxacalcitriol*** had no effect on [Ca2+]i at any concentration.(ABSTRACT TRUNCATED AT 250 WORDS)

L8 ANSWER 27 OF 32 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 93373844 MEDLINE
DOCUMENT NUMBER: 93373844 PubMed ID: 8396012
TITLE: The mechanism for the disparate actions of calcitriol and ***22*** - ***oxacalcitriol*** in the intestine.
AUTHOR: Brown A J; Finch J; Grieff M; Ritter C; Kubodera N; Nishii Y; Slatopolsky E
CORPORATE SOURCE: Renal Division, Washington University School of Medicine, St. Louis, Missouri 63110.
CONTRACT NUMBER: NIDDK DK-07126 (NIDDK)
NIDDK DK-09976 (NIDDK)
NIDDK DK-30178 (NIDDK)
SOURCE: ENDOCRINOLOGY, (1993 Sep) 133 (3) 1158-64.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931022
Last Updated on STN: 20030313
Entered Medline: 19931006
AB ***22*** - ***Oxacalcitriol*** (OCT) is one of several new ***analogs*** of ***vitamin*** ***D*** that retain many of the therapeutically useful properties of 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3], but have much less calcemic activity. In the present study we examined the actions of OCT on intestinal calcium absorption and calbindin D9k mRNA in ***vitamin*** ***D*** -deficient rats. After ip injection of OCT (1 microgram/kg), calcium absorption increased significantly by 2 h and was maximal at 4 h (2.5-fold above control), but returned to pretreatment levels by 16 h. In contrast, the same dose of 1,25-(OH)2D3 caused a 3-fold increase in calcium absorption, which lasted more than 48 h. The transient effect of OCT on calcium absorption was also observed when the analog was infused at a dose of 1 micrograms/kg.day for 3 days. At the end of the infusion period, calcium absorption was 3-fold higher than that in vehicle-infused controls, but fell to pretreatment levels by 24 h after removing the minipumps. The time courses for induction of calbindin D9k mRNA were similar for OCT and 1,25-(OH)2D3, with no change observed until more than 4 h after injection. However, calbindin mRNA levels returned to pretreatment values more rapidly in the OCT-treated rats. Consistent with these findings, we observed that a 1 microgram/kg dose of [3H] OCT was completely cleared by 4-6 h after injection. This was paralleled by a loss of [3H]OCT associated with the intestinal ***vitamin*** ***D*** receptor. The rapid clearance of OCT is probably due to its low affinity for the serum ***vitamin*** ***D*** -binding protein. This low affinity would also be expected to allow greater accessibility to target cells. In support of this, we found that higher amounts of OCT than 1,25-(OH)2D3 were associated with the intestinal ***vitamin*** ***D*** receptor after the injection of several doses of these tritiated ligands. In summary, our results indicate that the pharmacokinetic properties of OCT are responsible at least in part for its low calcemic activity. Furthermore, comparison of the transient elevation of calcium absorption by OCT with its more prolonged effects on ***PTH*** and calbindin D9k indicates that each action of ***vitamin*** ***D*** compounds has a distinct biological half-life. The short circulating half-life of OCT can exploit these differences to provide a therapeutic advantage in the treatment of ***vitamin*** ***D*** -responsive diseases.

L8 ANSWER 28 OF 32 MEDLINE on STN
ACCESSION NUMBER: 92283163 MEDLINE
DOCUMENT NUMBER: 92283163 PubMed ID: 1597134

TITLE: The effect of ***22*** - ***oxacalcitriol*** on serum calcitriol.
AUTHOR: Dusso A S; Negrea L; Finch J; Kamimura S; Lopez-Hilker S; Mori T; Nishii Y; Brown A; Slatopolsky E
CORPORATE SOURCE: Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri 63110.
CONTRACT NUMBER: DK-07126 (NIDDK)
DK-09976 (NIDDK)
DK-30178 (NIDDK)
SOURCE: ENDOCRINOLOGY, (1992 Jun) 130 (6) 3129-34.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920717
Last Updated on STN: 20030313
Entered Medline: 19920706

AB 1,25-Dihydroxyvitamin D3 (1,25D) regulates its own levels in circulation by affecting its rates of synthesis and degradation, ***22*** - ***Oxacalcitriol*** (OCT), a ***vitamin*** ***D*** analog with low calcemic activity, decreases circulating ***PTH*** levels, one of the regulators of renal 1 alpha-hydroxylase, and stimulates ***vitamin*** ***D*** degradation in vitro. The purpose of this study was to examine the effects of OCT administration on serum levels of 1,25D. In normal rats, OCT administration (4-200 ng, ip, daily for 5 days) caused a dose-dependent reduction in serum calcitriol levels. At a dose of 200 ng, OCT reduced serum 1,25D from 34.5 +/- 2.7 to 10.9 +/- 0.7 pg/ml (P less than or equal to 0.01) without significant changes in ionized Ca or phosphorus levels. The contribution of the suppression of ***PTH*** by OCT to the reduction of serum 1,25D was examined by administering OCT to parathyroidectomized (PTX) rats. Two hundred nanograms of OCT, ip, daily for 5 days significantly reduced serum calcitriol from 29.7 +/- 7.6 to 9.1 +/- 0.5 pg/ml (P less than or equal to 0.01) in rats fed a normal calcium diet. Because OCT increased total calcium (TCa) in this group from 7.4 +/- 0.1 to 9.5 +/- 0.3 mg/dl, similar doses of OCT were given to PTX rats fed a calcium-deficient diet. OCT decreased 1,25D from 58.9 +/- 8.9 to 10.3 +/- 0.4 pg/ml and increased TCa from 4.8 +/- 0.2 to 7.4 +/- 0.1 mg/dl. Comparison of serum 1,25D for identical TCa levels in PTX rats (normal calcium diet controls vs. calcium-deficient diet, OCT-treated) clearly indicates that OCT per se reduced serum 1,25D. Further support for a direct effect of OCT was provided by studies in PTX rats fed a low phosphorus diet. OCT decreased serum 1,25D from 125.8 +/- 15.6 to 10.9 +/- 0.6 pg/ml without significant changes in TCa. To further characterize the mechanisms involved in this effect, similar studies were performed in six normal dogs. Intravenous administration of 0.75 micrograms OCT every other day for 1 week decreased serum calcitriol from 25.4 +/- 3.2 to 12.2 +/- 1.3 pg/ml (P less than or equal to 0.002). Ionized Ca and phosphorus remained unchanged. Despite the short half-life of OCT in the circulation, 1,25D levels returned to basal concentrations 96 h after the last dose of OCT.(ABSTRACT TRUNCATED AT 400 WORDS)

L8 ANSWER 29 OF 32 MEDLINE on STN
ACCESSION NUMBER: 93112042 MEDLINE
DOCUMENT NUMBER: 93112042 PubMed ID: 1472047
TITLE: Metabolism of ***22*** - ***oxacalcitriol*** by a ***vitamin*** ***D*** -inducible pathway in cultured parathyroid cells.
AUTHOR: Brown A J; Berkoben M; Ritter C; Kubodera N; Nishii Y; Slatopolsky E
CORPORATE SOURCE: Renal Division, Washington University School of Medicine, St. Louis, MO 63110.
CONTRACT NUMBER: DK-07126 (NIDDK)
DK-09976 (NIDDK)
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1992

Dec 15) 189 (2) 759-64.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199301
ENTRY DATE: Entered STN: 19930212
Last Updated on STN: 20030313
Entered Medline: 19930128

AB Catabolism of ***22*** - ***oxacalcitriol*** (OCT) in parathyroid cells was compared to that of the parent hormone, 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3]. Catabolism of both compounds was greatly accelerated by pretreatment of the cells with 1,25-(OH)2D3 or OCT. The rate of degradation of OCT was slightly greater than that of 1,25-(OH)2D3. Excess unlabeled OCT or 1,25-(OH)2D3 inhibited metabolism of both tritiated substrates. Ketoconazole, a cytochrome P450 inhibitor, blocked catabolism of both compounds. The major OCT metabolite appeared to be 1,20-dihydroxy-22,23,24,25,26,27-hexanor-vitamin D3 which was not active in suppressing ***PTH*** secretion. We conclude that OCT appears to be metabolized by the same ***vitamin*** ***D*** -inducible side chain oxidation pathway that catabolizes other ***vitamin*** ***D*** compounds and that its higher than expected suppression of ***PTH*** secretion is not due to slower cellular metabolism.

L8 ANSWER 30 OF 32 MEDLINE on STN

ACCESSION NUMBER: 91309560 MEDLINE
DOCUMENT NUMBER: 91309560 PubMed ID: 1649745

TITLE: The activity of ***22*** - ***oxacalcitriol*** in osteoblast-like (ROS 17/2.8) cells.

AUTHOR: Pemalete N; Mori T; Nishii Y; Slatopolsky E; Brown A J
CORPORATE SOURCE: Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110.

CONTRACT NUMBER: DK-07126 (NIDDK)
DK-09976 (NIDDK)
DK-30178 (NIDDK)
SOURCE: ENDOCRINOLOGY, (1991 Aug) 129 (2) 778-84.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910913
Last Updated on STN: 20030313
Entered Medline: 19910828

AB ***22*** - ***Oxacalcitriol*** (OCT), a synthetic ***vitamin*** ***D*** analog, can mimic the ability of 1,25-dihydroxyvitamin D3[1,25-(OH)2D3] to differentiate leukemia and skin cells, to enhance the immune response and to suppress ***PTH*** secretion, but has much less calcemic activity. The mechanism for this selective action is not understood. OCT has been shown to have a diminished ability to mobilize calcium from bone in vivo, but in vitro findings are contradictory. Little is known about the effect of OCT on bone forming cells. Therefore, the present studies were designed to investigate the actions of OCT at the molecular level in the osteoblast-like cell line, ROS 17/2.8. 3H-OCT was bound to the ***vitamin*** ***D*** receptor (VDR) in intact cells at the same rate as 3H-1,25-(OH)2D3. As previously found for 1,25-(OH)2D3, the time course of specific binding of OCT was biphasic, with an initial plateau at 1 h and a further increase from 2-8 h. Scatchard analysis demonstrated that exposure to 3H-1,25-(OH)2D3 increased VDR from 24 fmol/mg protein at 2 h to 85 fmol/mg protein at 8 h. Exposure to 3H-OCT increased VDR from 22 to 76 fmol/mg protein, indicating that OCT is also capable of up-regulating the VDR in ROS 17/2.8 cells. In contrast to the lower affinity of OCT for VDR reported for chick intestine and HL-60 cells, the Kd for OCT in intact ROS 17/2.8 cells was identical to that for 1,25-(OH)2D3. The effect of OCT on osteocalcin secretion and

alkaline phosphatase (ALP) activity in ROS 17/2.8 cells was also determined. Pretreatment for 24 h with either 1,25-(OH)2D3 or OCT resulted in a dose-dependent enhancement of osteocalcin secretion. A 2-fold stimulation by both compounds was observed with 10(-7)M. ALP activity was measured after a 72-h incubation with 10(-7)M 1,25-(OH)2D3 or OCT. Both compounds increased ALP activity to the same extent. Stimulation by OCT of VDR levels, ALP activity, and osteocalcin secretion were inhibited by the addition of 5 microM cycloheximide, indicating that these actions of OCT require new protein synthesis. Thus, OCT, like 1,25-(OH)2D3, up-regulates the ***vitamin*** ***D*** receptor, stimulates osteocalcin secretion, and increases ALP activity in ROS 17/2.8 cells, suggesting that the analog may be as active as 1,25-(OH)2D3 in stimulating bone formation in vivo. The low activity of OCT in mobilizing calcium from bone in vivo does not appear to be due to an inability of this compound to act on osteoblasts.

L8 ANSWER 31 OF 32 MEDLINE on STN
ACCESSION NUMBER: 92191635 MEDLINE
DOCUMENT NUMBER: 92191635 PubMed ID: 1800003
TITLE: The noncalcemic analogue of ***vitamin*** ***D*** , ***22*** - ***oxacalcitriol*** , suppresses parathyroid hormone synthesis and secretion.
AUTHOR: Nishii Y; Abe J; Mori T; Brown A J; Dusso A S; Finch J; Lopez-Hilker S; Morrissey J; Slatopolsky E
CORPORATE SOURCE: Research Laboratory of Chugai Pharmaceutical Co., Tokyo, Japan.
SOURCE: CONTRIBUTIONS TO NEPHROLOGY, (1991) 91 123-8. Ref: 9
Journal code: 7513582. ISSN: 0302-5144.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920509
Last Updated on STN: 20030313
Entered Medline: 19920421
AB OCT, a non-calcemic analogue of 1,25(OH)2D3 has been found to have a more potent activity than that of 1,25(OH)2D3 regarding cell differentiation and immunopotentiation activity, and to prolong the average life span of MRL/l mice. Recently, we found that OCT effectively suppressed the secretion and synthesis of ***PTH*** without inducing hypercalcemia. In primary cultures of bovine parathyroid cells, OCT was capable of suppressing ***PTH*** release in a dose-dependent manner. OCT was also active in vivo, and, like 1,25(OH)2D3, decreased the pre-pro(***PTH***) mRNA levels. In a group of rats with CRF, daily administration of OCT, 8 ng i.p. for 2 weeks returned ***PTH*** levels to normal without changes in serum calcium. Preliminary results in dogs with CRF indicated that after the administration of OCT 5 micrograms i.v., N-terminal ***PTH*** decreased by 76% without changes in Ca. In conclusion, OCT may provide a unique contribution to the treatment of secondary hyperparathyroidism.

L8 ANSWER 32 OF 32 MEDLINE on STN
ACCESSION NUMBER: 89340905 MEDLINE
DOCUMENT NUMBER: 89340905 PubMed ID: 2760211
TITLE: The noncalcemic analogue of ***vitamin*** ***D*** , ***22*** - ***oxacalcitriol*** , suppresses parathyroid hormone synthesis and secretion.
AUTHOR: Brown A J; Ritter C R; Finch J L; Morrissey J; Martin K J; Murayama E; Nishii Y; Slatopolsky E
CORPORATE SOURCE: Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1989 Sep) 84 (3) 728-32.
Journal code: 7802877. ISSN: 0021-9738.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198909
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 20030313
Entered Medline: 19890921

AB 1,25-Dihydroxyvitamin D (1,25-(OH)2D3) directly suppresses the secretion and synthesis of ***PTH*** in vivo and in cell culture. This compound has been used to treat secondary hyperparathyroidism associated with renal failure, but in some patients prolonged treatment with 1,25-(OH)2D3 results in hypercalcemia. An analogue of 1,25-(OH)2D3 with little or no calcemic activity, ***22*** - ***oxacalcitriol*** (OCT), was recently developed. We confirmed this lack of calcemic activity by acute and chronic administration to normal rats. A single intraperitoneal injection of vehicle (propylene glycol), OCT, or 1,25-(OH)2D3 (1.0 micrograms/rat) increased calcium by 0.32, 0.30, and 1.40 mg/dl, respectively. When rats were given daily injections of vehicle or 0.5 micrograms of either 1,25-(OH)2D3 or OCT for 4 d, calcium did not change in the rats receiving vehicle or OCT, but increased from 8.4 to 11.4 mg/dl in the rats treated with 1,25-(OH)2D3. In primary cultures of bovine parathyroid cells, 10 nM OCT was as active as 10 nM 1,25-(OH)2D3, suppressing ***PTH*** release by 33%. This suppression is due, at least in part, to blocking of transcription of the ***PTH*** gene. Using a probe prepared by random prime labeling of an Msp I fragment of plasmid PTHm122, we found that a single 40-ng dose of OCT or 1,25-(OH)2D3 depressed ***PTH*** mRNA levels by 70-80% by 48 h when compared with vehicle. Thus, OCT is a very effective suppressor of ***PTH*** secretion with virtually no calcemic activity. This analogue may be a valuable tool for the treatment of secondary hyperparathyroidism.

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(FILE 'HOME' ENTERED AT 13:53:44 ON 02 OCT 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 13:53:54 ON 02 OCT 2003
L1 91158 S VITAMIN D
L2 583 S 22-OXACALCITRIOL
L3 368 S L1 AND L2
L4 40950 S PTH
L5 108 S L3 AND L4
L6 581671 S ANALOGS
L7 46 S L5 AND L6
L8 32 DUP REM L7 (14 DUPLICATES REMOVED)

colchicine.
AUTHOR: Grone A; Weckmann M T; Capen C C; Rosol T J
CORPORATE SOURCE: Department of Veterinary Biosciences, The Ohio State University, Columbus, USA.
CONTRACT NUMBER: AR01923 (NIAMS)
AR40220 (NIAMS)
SOURCE: EXPERIMENTAL AND TOXICOLOGIC PATHOLOGY, (1998 Sep) 50 (4-6) 365-70.
Journal code: 9208920. ISSN: 0940-2993.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981218
AB The regulation of parathyroid hormone-related protein expression by colchicine, vinblastine, nocodazole, taxol, transforming growth factor-beta1 (TGFbeta1), and epidermal growth factor (EGF) was investigated in a canine squamous carcinoma cell line (SCC 2/88 cells). SCC 2/88 cells were stably transfected with a human P2/P3 ***PTHrP*** ***promoter*** -luciferase reporter gene construct and ***gene*** ***expression*** was measured after chemical treatments. The greatest increase in reporter ***gene*** ***expression*** was observed after colchicine treatment and small increases occurred after treatment with vinblastine, taxol, TGFbeta1, or EGF. Nocodazole had no significant effect on reporter ***gene*** ***expression*** . Colchicine also increased ***PTHrP*** steady state mRNA expression and ***PTHrP*** secretion by SCC 2/88 cells. These results demonstrated that ***PTHrP*** production was increased in SCC 2/88 cells by colchicine and suggested that factors or events during mitosis are capable of stimulating ***PTHrP*** production. An increase in ***PTHrP*** production during mitosis of malignant epithelial cells may be important in the pathogenesis of ***humoral*** ***hypercalcemia*** of ***malignancy*** .

L19 ANSWER 6 OF 16 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 97254495 MEDLINE
DOCUMENT NUMBER: 97254495 PubMed ID: 9099905
TITLE: The noncalcemic vitamin D analogues EB1089 and 22-oxacalcitriol interact with the vitamin D receptor and suppress parathyroid hormone-related peptide ***gene*** ***expression*** .
AUTHOR: Falzon M
CORPORATE SOURCE: Department of Pharmacology and Toxicology, and Sealy Center for Molecular Science, The University of Texas Medical Branch, Galveston 77555, USA.
SOURCE: MOLECULAR AND CELLULAR ENDOCRINOLOGY, (1997 Mar 14) 127 (1) 99-108.
Journal code: 7500844. ISSN: 0303-7207.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 20030313
Entered Medline: 19970617
AB ***Humoral*** ***hypercalcemia*** of ***malignancy*** , a frequent complication of squamous cell carcinomas of the lung, is mediated by the parathyroid hormone-related peptide (***PTHrP***). This study was undertaken to determine whether 1,25-dihydroxyvitamin D(3) [1,25(OH)(2)D(3)] and two nonhypercalcemic analogues. EB1089 and 22-oxa-1,25(OH)(2)D(3) (OCT), suppress ***PTHrP*** ***gene*** ***expression*** in a human lung squamous cancer cell line, NCI H520. All three compounds (1) decreased steady-state ***PTHrP*** mRNA and

secreted peptide levels via a transcriptional mechanism; (2) modulated ***promoter*** activity of 1,25(OH)(2)D(3)-responsive DNA sequences; and (3) activated the vitamin D receptor (VDR) both in vitro and in vivo. Thus, EB1089 and OCT inhibit ***PTHrP*** ***gene*** ***expression*** in NCI H520 cells and modulate ***gene*** ***expression*** through the same mechanism as 1,25(OH)(2)D(3), namely, activation of the VDR. 1,25(OH)(2)D(3) is hypercalcemic in vivo. However, the noncalcemic analogues EB1089 and OCT have a therapeutic potential through suppression of ***PTHrP*** gene transcription.

L19 ANSWER 7 OF 16 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 96234380 MEDLINE
DOCUMENT NUMBER: 96234380 PubMed ID: 8640759
TITLE: Transactivation of the ***PTHrP*** gene in squamous carcinomas predicts the occurrence of hypercalcemia in athymic mice.
AUTHOR: Wysolmerski J J; Vasavada R; Foley J; Weir E C; Burtis W J; Kukreja S C; Guise T A; Broadus A E; Philbrick W M
CORPORATE SOURCE: Department of Medicine, Yale University School of Medicine, New Haven, Connecticut 06510, USA.
CONTRACT NUMBER: CA 09331 (NCI)
SOURCE: CANCER RESEARCH, (1996 Mar 1) 56 (5) 1043-9.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960726
Last Updated on STN: 19970203
Entered Medline: 19960715
AB ***Humoral*** ***hypercalcemia*** of ***malignancy*** (***HHM***) is caused by the secretion of parathyroid hormone-related protein (***PTHrP***) by tumor cells, and tumors of squamous histology are the ones most commonly complicated by ***HHM*** . To determine why some squamous tumors cause ***HHM*** and others do not, we quantitated the levels of ***PTHrP*** mRNA expression and ***PTHrP*** secretion in a series of eight squamous tumor lines. As anticipated, we found that the level of ***PTHrP*** mRNA expression in individual lines correlated with their ***PTHrP*** secretion rates. However, ***PTHrP*** mRNA levels varied widely in individual lines, and only those tumor lines with the highest levels of ***PTHrP*** ***gene*** ***expression*** were able to cause hypercalcemia in athymic mice. We found that a specific segment of the ***PTHrP*** ***promoter*** could reproduce the relative pattern of ***PTHrP*** ***gene*** ***expression*** when cloned in front of a chloramphenicol acetyltransferase reporter gene and transiently transfected into these squamous lines. Deletional analysis confirmed that specific sequences within the ***PTHrP*** gene ***promoter*** appeared to be involved in the transactivation of the gene in tumor lines expressing high levels of ***PTHrP*** mRNA. These data suggest that the ability of a given squamous tumor to cause ***HHM*** is ultimately a function of its level of ***PTHrP*** ***gene*** ***expression*** , which in turn appears to be a function of the ability of specific transcription factors to transactivate ***PTHrP*** ***gene*** ***expression***
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L19 ANSWER 8 OF 16 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 96372974 MEDLINE
DOCUMENT NUMBER: 96372974 PubMed ID: 8776727
TITLE: DNA sequences in the rat parathyroid hormone-related peptide gene responsible for 1,25-dihydroxyvitamin D3-mediated transcriptional repression.
AUTHOR: Falzon M
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston 77555, USA.
SOURCE: MOLECULAR ENDOCRINOLOGY, (1996 Jun) 10 (6) 672-81.

Journal code: 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961230

AB Expression of the gene encoding PTH-related peptide (***PTHrP***), a protein that plays a primary role in the development of ***humoral*** ***hypercalcemia*** of ***malignancy*** , is down-regulated at the transcriptional level by 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3]. Deletions of the 5'-flanking region of the rat ***PTHrP*** gene, when fused to the chloramphenicol acetyl-transferase gene and transfected into ROS 17/2.8 (rat osteosarcoma) cells, showed that the 1,25-(OH)2D3 responsive region is located between -1.05 and -0.71 kb upstream of the transcription start site. Further mapping of this region revealed that a 123-bp fragment is able to confer 1,25-(OH)2D3 responsiveness to a heterologous (SV40) ***promoter*** . This region contains two potential vitamin D response elements (VDREs). One of these motifs resembles the negative VDRE (nVDRE) from the PTH gene, which is also down-regulated by vitamin D3. The other element resembles the canonical VDRE (two hexanucleotide motifs separated by three nucleotides), which has been characterized in a number of genes whose expression is modulated by vitamin D3. Electrophoretic mobility shift assays using nuclear extracts from ROS 17/2,8 cells and from vitamin D receptor. (VDR)-enriched COS 1 cells revealed that both elements interact with the VDR. This protein-DNA interaction is disrupted by an anti-VDR antibody. Therefore, modulation of ***PTHrP*** gene transcription by 1,25-(OH)2D3 is mediated by the VDR interacting with one or both of the identified motifs in the 5'-flanking sequence of the gene.

L19 ANSWER 9 OF 16 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 96125057 MEDLINE
DOCUMENT NUMBER: 96125057 PubMed ID: 8537338
TITLE: Neoplastic transformation of normal rat embryo fibroblasts by a mutated p53 and an activated ras oncogene induces parathyroid hormone-related peptide ***gene*** ***expression*** and causes hypercalcemia in nude mice.
AUTHOR: Motokura T; Endo K; Kumaki K; Ogata E; Ikeda K
CORPORATE SOURCE: Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Dec 29) 270 (52) 30857-61.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960221
Last Updated on STN: 19960221
Entered Medline: 19960208

AB Parathyroid hormone-related peptide (***PTHRP***) is a 141-amino acid protein identified in various carcinomas associated with ***humoral*** ***hypercalcemia*** of ***malignancy*** (***HHM***). Although the causal role of ***PTHRP*** in ***HHM*** syndrome has been established, the molecular and cellular mechanism by which ***PTHRP*** gene is overexpressed in certain malignancies remains unknown. We have demonstrated in the present study that ***PTHRP*** secretion was markedly induced concomitantly with the formation of transformed foci after normal rat embryo fibroblasts (REFs) were co-transfected with an activated ras (ras) and a mutated form of p53 (p53-mt) genes. In either ras- or p53-mt-transfected (nontransformed) cells, only modest or barely detectable secretion of ***PTHRP*** was observed, respectively. Northern blot analysis revealed that ***PTHRP*** mRNA was markedly

induced in fully transformed cells 11 days after transfection with both ras and p53-mt genes. Inhibition of RNA synthesis with actinomycin D resulted in almost complete disappearance of ***PTHRP*** mRNA at 2-3 h, suggesting a transcriptional mechanism. Transient transfection experiments revealed that ***PTHRP*** ***promoter*** activity was induced in ras + p53-mt transfectants. REFs transformed by ras and p53-mt genes and thereby induced to secrete ***PTHRP*** in vitro produced aggressively growing tumors associated with ***HHM*** syndrome when injected into nude mice. These results suggest that activation of ***PTHRP*** gene is closely related to malignant transformation of normal mammalian cells and that ras and p53 may be important regulators of ***PTHRP*** gene transcription. The transfection-focus formation system of REFs should provide an excellent model to study the molecular and cellular mechanism underlying concomitant overexpression of ***PTHRP*** gene with carcinogenesis.

L19 ANSWER 10 OF 16 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 95266471 MEDLINE
DOCUMENT NUMBER: 95266471 PubMed ID: 7747629
TITLE: In vivo evidence for progressive activation of parathyroid hormone-related peptide gene transcription with tumor growth and stimulation of osteoblastic bone formation at an early stage of humoral hypercalcemia of cancer.
AUTHOR: Yamato H; Nagai Y; Inoue D; Ohnishi Y; Ueyama Y; Ohno H; Matsumoto T; Ogata E; Ikeda K
CORPORATE SOURCE: Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Japan.
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (1995 Jan) 10 (1) 36-44.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950621
Last Updated on STN: 19950621
Entered Medline: 19950612
AB The present study was undertaken to clarify in vivo the temporal profile of parathyroid hormone-related peptide (***PTHRP***) ***gene*** ***expression*** as well as bone histomorphometric features as a function of tumor growth, using an athymic rat model associated with ***humoral*** ***hypercalcemia*** of ***malignancy*** (***HHM***). Tumor-bearing animals exhibited hypercalcemia, hypophosphatemia, and increased circulating levels of ***PTHRP*** , and died within 3 weeks. Steady-state ***PTHRP*** mRNA levels and the transcription rate of ***PTHRP*** gene in the tumors were markedly increased with tumor growth. RNAse mapping analysis revealed that both upstream and downstream promoters of the human ***PTHRP*** gene were utilized in the tumors and became progressively activated with time. Bone histomorphometric analysis showed that osteoclastic bone resorption was progressively increased throughout the course, whereas osteoblastic bone formation was stimulated more than 2-fold at a very early stage (day 6 after tumor implantation) and then markedly suppressed thereafter on day 12 and day 18 compared with age-matched control animals. These results provide in vivo evidence that ***PTHRP*** gene transcription is progressively activated with tumor growth and that activation of osteoblasts does occur at a very early phase of ***HHM*** syndrome in contrast to the marked suppression of bone formation at later stages.

L19 ANSWER 11 OF 16 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 94134712 MEDLINE
DOCUMENT NUMBER: 94134712 PubMed ID: 7508121
TITLE: Overexpression of parathyroid hormone-related protein in the skin of transgenic mice interferes with hair follicle development.
AUTHOR: Wysolmerski J J; Broadus A E; Zhou J; Fuchs E; Milstone L

M; Philbrick W M
CORPORATE SOURCE: Department of Medicine, Yale University School of Medicine, New Haven, CT 06510.
CONTRACT NUMBER: AR 37594 (NIAMS)
AR30102 (NIAMS)
CA 09331 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Feb 1) 91 (3) 1133-7.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940318
Last Updated on STN: 19960129
Entered Medline: 19940308
AB Parathyroid hormone-related peptide (***PTHrP***) was initially discovered as the cause of the syndrome of ***humoral*** ***hypercalcemia*** of ***malignancy*** . Subsequently, the ***PTHrP*** gene has been shown to be expressed in a wide variety of normal tissues, including skin. Because the biological function of ***PTHrP*** in skin remains unknown, we used the human keratin 14 ***promoter*** to target overexpression of ***PTHrP*** to the skin of transgenic mice. We achieved a 10-fold level of overexpression in skin, and human keratin 14 ***promoter*** - ***PTHrP*** transgenic mice displayed a disturbance in normal hair follicle development. These mice either failed to initiate follicle development or showed a delay in the initiation of follicles. These findings suggest that ***PTHrP*** normally plays a role in the early stages of hair follicle development and support previous speculation that the peptide may function in regulating cellular differentiation.

L19 ANSWER 12 OF 16 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 93388646 MEDLINE
DOCUMENT NUMBER: 93388646 PubMed ID: 7690760
TITLE: Region-specific methylation of the parathyroid hormone-related peptide gene determines its expression in human renal carcinoma cell lines.
AUTHOR: Holt E H; Vasavada R C; Bander N H; Broadus A E; Philbrick W M
CORPORATE SOURCE: Department of Internal Medicine, Yale University, New Haven, Connecticut 06510.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 Sep 25) 268 (27) 20639-45.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931105
Last Updated on STN: 19980206
Entered Medline: 19931020
AB Tumor production of a parathyroid hormone-related peptide (***PTHrP***) is a common cause of the syndrome of ***humoral*** ***hypercalcemia*** of ***malignancy*** , which is frequently associated with renal cell carcinomas. Why certain renal cell carcinomas produce ***PTHrP*** while others do not is unknown. Using a system of 12 human renal carcinoma cell lines which either do (n = 6) or do not (n = 6) produce ***PTHrP*** , we found that the expression of the ***PTHrP*** gene in these cell lines is controlled at the transcriptional level. Transfection studies failed to demonstrate variation in ***PTHrP*** ***promoter*** activity in these cell lines sufficient to account for the differential ***PTHrP*** expression, implicating a cis-acting mechanism. Transcription of the ***PTHrP*** gene in these cell lines was found to correlate with the

methylation state of specific CpG dinucleotides located within the ***promoter*** region but outside a CpG island. The functional importance of this mechanism of control was confirmed by the ability of the demethylating agent, 5-azacytidine, to induce ***PTHrP*** mRNA expression in previously nonexpressing cell lines.

L19 ANSWER 13 OF 16 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 93277534 EMBASE
DOCUMENT NUMBER: 1993277534
TITLE: Transactivation of the P2 ***promoter*** of parathyroid hormone-related protein by human T-cell lymphotropic virus type I Tax1: Evidence for the involvement of transcription factor Ets1.
AUTHOR: Dittmer J.; Gitlin S.D.; Reid R.L.; Brady J.N.
CORPORATE SOURCE: Laboratory of Molecular Virology, National Cancer Institute,Bethesda, MD 20892, United States
SOURCE: Journal of Virology, (1993) 67/10 (6087-6095).
ISSN: 0022-538X CODEN: JOVIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Expression of the parathyroid hormone-related protein (***PTHrP***), a protein that plays a primary role in the development of the ***humoral*** ***hypercalcemia*** of ***malignancy*** , is regulated by two distinct promoters, P1 and P2. ***PTHrP*** is overexpressed in lymphocytes from adult T-cell leukemia patients. We now demonstrate that in the human T-cell lymphotropic virus type I-transformed cell line MT-2, RNA synthesis is initiated primarily at the P2 ***promoter*** . Furthermore, in cotransfection experiments, Tax1 transactivates the P2 ***promoter*** 10- to 12-fold. By using deletion and site-specific point mutations, we have identified a ***promoter*** -proximal sequence (positions -72 to -40) which is important for Tax1 transactivation. The ***PTHrP*** ***promoter*** - proximal element contains two potential overlapping Ets1 binding sites, EBS I and EBS II. Gel shift analysis demonstrated that Ets1 binds specifically to both EBS I and EBS II. Mutation of the consensus GGAA core motif in EBS I abolished binding and Tax1 transactivation in Jurkat T lymphocytes. In Ets1-deficient cells, cotransfection of Tax1 and Ets1 expression plasmids stimulates ***PTHrP*** ***promoter*** activity. In the absence of Ets1, minimal transactivation of the ***PTHrP*** ***promoter*** is observed. These data suggest that Ets1 binds to EBS I and cooperates with Tax1 to transactivate the ***PTHrP*** P2 ***promoter*** .

L19 ANSWER 14 OF 16 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 90202767 MEDLINE
DOCUMENT NUMBER: 90202767 PubMed ID: 2318820
TITLE: Regulation of parathyroid hormone-related peptide ***gene*** ***expression*** by cycloheximide.
AUTHOR: Ikeda K; Lu C; Weir E C; Mangin M; Broadus A E
CORPORATE SOURCE: Department of Internal Medicine, Yale University, New Haven, Connecticut 06510.
CONTRACT NUMBER: AR-30102 (NIAMS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1990 Apr 5) 265 (10) 5398-402.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199005
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 19970203
Entered Medline: 19900503

AB A novel parathyroid hormone-related peptide (***PTHRP***) has been isolated from tumors associated with the syndrome of ***humoral*** ***hypercalcemia*** of ***malignancy*** . The human ***PTHRP*** gene appears to use multiple promoters and contains alternatively spliced 3' exons which give rise to three ***PTHRP*** mRNA classes, each bearing multiple copies of an AU motif that has been associated with mRNA instability. We report here that inhibition of protein synthesis leads to the super-induction of ***PTHRP*** mRNA expression in a number of human and rat cell lines. This phenomenon was found to reflect both an increase in the rate of ***PTHRP*** gene transcription and a stabilization of ***PTHRP*** mRNAs. The transcriptional mechanism appears to preferentially involve the activity of a short downstream ***promoter*** of the gene, which is presumed to be regulated by a labile repressor protein. Our findings indicate that both transcriptional and posttranscriptional mechanisms may be important control points in the regulation of ***PTHRP*** expression in normal and malignant cells.

L19 ANSWER 15 OF 16 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 91065532 MEDLINE
DOCUMENT NUMBER: 91065532 PubMed ID: 2249778
TITLE: Structure of the mouse gene encoding parathyroid hormone-related peptide.
AUTHOR: Mangin M; Ikeda K; Broadus A E
CORPORATE SOURCE: Department of Internal Medicine, Yale University, New Haven, CT 06510.
CONTRACT NUMBER: AR-30102 (NIAMS)
SOURCE: GENE, (1990 Nov 15) 95 (2) 195-202.
Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M34098; GENBANK-M34099; GENBANK-M34100; GENBANK-M60056; GENBANK-M60057; GENBANK-M60058
ENTRY MONTH: 199101
ENTRY DATE: Entered STN: 19910308
Last Updated on STN: 19970203
Entered Medline: 19910116

AB The parathyroid hormone-related peptide (***PTHRP***) was initially isolated from tumors associated with the syndrome of ***humoral*** ***hypercalcemia*** of ***malignancy*** . The human ***PTHRP*** gene is a complex transcriptional unit which uses multiple promoters and contains alternatively spliced 3' exons that result in mRNAs encoding three different deduced products. We report here the structure of the mouse ***PTHRP*** gene. The mouse gene has a considerably simpler organization than its human counterpart. This organization includes a single 3' exon and an apparent single 3' splicing pathway, leading to an mRNA encoding a 139-amino acid mature ***PTHRP*** . In addition, the mouse gene appears to be predominantly under the control of a short proximal ***promoter*** element. By RNase protection analysis, we identified ***PTHRP*** mRNA in specimens prepared from a variety of normal rodent tissues, including a number of tissues not previously recognized as sites of ***PTHRP*** ***gene*** ***expression*** .

L19 ANSWER 16 OF 16 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 90062428 MEDLINE
DOCUMENT NUMBER: 90062428 PubMed ID: 2573615
TITLE: Expression of transcripts encoding a parathyroid hormone-related peptide in abnormal human parathyroid tissues.
AUTHOR: Ikeda K; Arnold A; Mangin M; Kinder B; Vydelingum N A; Brennan M F; Broadus A E
CORPORATE SOURCE: Department of Internal Medicine, Yale University, New Haven, Connecticut 06510.
CONTRACT NUMBER: AR-30102 (NIAMS)
DK-11794 (NIDDK)

SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, (1989 Dec) 69 (6) 1240-8.
Journal code: 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198912
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19970203
Entered Medline: 19891229

AB A PTH-related peptide (***PTHRP***) has been identified and its cDNA cloned from human tumors associated with the syndrome of ***humoral*** ***hypercalcemia*** of ***malignancy*** . The human ***PTHRP*** gene has been recently isolated and found to be a complex transcriptional unit using multiple promoters and containing alternatively spliced 3' exons which result in three mRNA classes, each class encoding a ***PTHRP*** with a unique carboxy-terminus. The ***PTHRP*** gene appears to be expressed in a number of normal tissues, and ***PTHRP*** transcripts have been previously reported to be overexpressed in a small sample of human parathyroid adenomas. In the present study we surveyed RNA prepared from a total of 60 abnormal human parathyroid glands for ***PTHRP*** ***gene*** ***expression*** using a combination of Northern blotting and RNase protection techniques. Apparent overexpression of ***PTHRP*** mRNA was observed in two thirds of parathyroid adenomas, whereas no overexpression was found in 7 examples of sporadic primary hyperplasia, 5 examples of secondary hyperplasia, and 3 examples of parathyroid carcinoma. Apparent overexpression was also observed in 1 of 4 cases of multiple endocrine neoplasia type 1, 1 of 2 examples of multiple endocrine neoplasia type 2, and 1 gland considered to represent tertiary hyperparathyroidism. Northern analysis of poly(A)+ RNA prepared from three representative adenomas using region-specific probes indicated that two putative promoters are used and revealed a pattern of preferential splicing of transcripts to include the most distal 3' exon. These findings suggest that the ***PTHRP*** gene is commonly overexpressed in adenomatous parathyroid glands, but not in sporadic primary hyperplasia, that this overexpression does not seem to be dependent on the use of a single specific ***promoter*** , and that adenomatous parathyroid cells appear to preferentially use one of several alternative splicing pathways. It is presently not known whether ***PTHRP*** is secreted by abnormal parathyroid tissues and, if so, in what form.

LANGUAGE: English

L10 ANSWER 48 OF 54 MEDLINE
ACCESSION NUMBER: 89380153 MEDLINE
DOCUMENT NUMBER: 89380153 PubMed ID: 2777759
TITLE: Transcriptional ***regulation*** of the ***parathyroid*** ***hormone*** - ***related*** ***peptide*** gene by glucocorticoids and vitamin D in a human C-cell line.
AUTHOR: Ikeda K; Lu C; Weir E C; Mangin M; Broadus A E
CORPORATE SOURCE: Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut 06510.
CONTRACT NUMBER: AR-30102 (NIAMS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, ***(1989 Sep 25)*** 264 (27) 15743-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198910
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19891025
AB A ***parathyroid*** ***hormone*** - ***related*** ***peptide*** (***PTHRP***) has been identified in human tumors associated with the syndrome of humoral ***hypercalcemia*** of malignancy. The ***PTHRP*** and parathyroid hormone (PTH) genes appear to have arisen by duplication and to represent members of a gene family. ***PTHRP*** mRNAs have been demonstrated in a number of normal tissues, but little is known concerning the regulation of ***PTHRP*** gene expression in any site. We studied ***PTHRP*** gene expression in TT cells, a human C-cell line which also produces calcitonin and calcitonin gene-related peptide. We found that both the synthetic glucocorticoid, dexamethasone, and the active vitamin D metabolite, 1,25-dihydroxyvitamin D3, decreased steady-state ***PTHRP*** mRNA levels in TT cells in a time- and dose-dependent fashion. The dexamethasone effect was completely blocked by the glucocorticoid antagonist RU-486. 24,25-dihydroxyvitamin D3 was found to be inactive. Neither dexamethasone nor 1,25-dihydroxyvitamin D3 appeared to influence ***PTHRP*** mRNA stability in TT cells, and both agents were shown by nuclear transcription run-off assay to decrease ***PTHRP*** gene transcription. These findings indicate that the ***PTHRP*** gene is under the transcriptional control of glucocorticoids and vitamin D in a cell line with prototypical neuroendocrine features.

order refs in red for amendment.

L10 ANSWER 49 OF 54 MEDLINE
ACCESSION NUMBER: 90190663 MEDLINE
DOCUMENT NUMBER: 90190663 PubMed ID: 2628737
TITLE: Glucocorticoid ***regulation*** of ***parathyroid*** ***hormone*** - ***related*** ***peptide*** gene transcription in a human neuroendocrine cell line.
AUTHOR: Lu C; Ikeda K; Deftos L J; Gazdar A F; Mangin M; Broadus A E
CORPORATE SOURCE: Department of Internal Medicine, Yale University, New Haven, Connecticutt 06511.
CONTRACT NUMBER: AR-15888 (NIAMS)
AR-30102 (NIAMS)
CA-49474 (NCI)
SOURCE: MOLECULAR ENDOCRINOLOGY, ***(1989 Dec)*** 3 (12) 2034-40.
Journal code: 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199004
ENTRY DATE: Entered STN: 19900601

Brown et al

09879445

CONTRACT NUMBER: AR 39571 (NIAMS)
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, ***(1990 Oct)***
5 (10) 1037-41.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199104
ENTRY DATE: Entered STN: 19910519
Last Updated on STN: 19910519
Entered Medline: 19910426

AB The enzyme carbonic anhydrase has been suggested as a critical participant in osteoclast-mediated bone resorption. In humoral ***hypercalcemia*** of malignancy (HHM) intense osteoclastic bone resorption is principally responsible for the observed ***hypercalcemia*** . We therefore undertook to examine the effect of the carbonic anhydrase inhibitor acetazolamide on the ***hypercalcemia*** induced by the H500 Leydig cell tumor in Fisher rats, a well-described model of HHM. Acetazolamide treatment for 10 h at 10 mg/h resulted in a significant fall in serum calcium in the five drug-treated animals (14.2 +/- 0.9 to 11.5 +/- 0.1 mg/dl, p less than 0.05). Conversely, the six animals infused with vehicle alone showed a significant rise in serum calcium (12.5 +/- 0.5 to 13.8 +/- 0.1 mg/dl, p less than 0.05). At the end of the infusion, the acetazolamide-treated animals had a significantly lower mean serum calcium than those receiving vehicle alone (11.5 +/- 0.1 versus 13.8 +/- 0.1, p less than 0.05). There was no significant change in serum phosphorus, urine calcium, urine phosphorus, or nephrogenous cyclic AMP excretion between the two groups. Acetazaolamide and HTS 5-(3-hydroxybenzoyl)-2-thiophenesulfonamide, another carbonic anhydrase inhibitor, both significantly inhibited in vitro bone resorption induced by 5 X 10(-9) M 36Tyr(1-36)- ***PTHrP*** -amide (***PTHrP*** , parathyroid hormone-related protein). Acetazolamide also inhibited the resorption induced by 10(-8) M (1-141)- ***PTHrP*** and 2.5 X 10(-9) M (1-74)- ***PTHrP*** . We conclude that acetazolamide is effective in lowering the serum calcium in animals with humoral ***hypercalcemia*** of malignancy. The data are consistent with the hypothesis that the mechanism of action for this effect is direct inhibition of osteoclast-mediated bone resorption.

L10 ANSWER 45 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1991:3211 BIOSIS
DOCUMENT NUMBER: BA91:3211
TITLE: HUMAN PTH-3-34 ***INHIBITED*** THE EFFECTS OF HUMAN PARATHYROID HORMONE-RELATED PROTEIN ON PHOSPHATE UPTAKE IN A CULTURED RENAL CELL LINE OK CELLS.
AUTHOR(S): NAKAI M; FUKASE M; YAMAGUCHI T; TSUKAMOTO T; FUJII N; FUJITA T
CORPORATE SOURCE: DEP. MED., DIV. ENDOCRINOL., TEX. HEALTH SCI. CENT. AT SAN ANTONIO, 7703 FLOYD CURL DR., SAN ANTONIO, TEX. 78284-7877, USA.
SOURCE: J BONE MINER RES, (1990) 5 (10), 995-1002.
CODEN: JBMREJ. ISSN: 0884-0431.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The action mechanism of hPTH and hPTHrP-(1-34) on phosphate uptake in opossum kidney (OK) cells was studied using [Nle8,18Tyr34]hPTH-(3-34)-NH2, a potent competitive inhibitor of adenylate cyclase-coupled PTH receptor. We examined the effects of hPTH-(1-34), hPTHrP-(1-34), and hPTH-(3-34) separately or in combination on the change in renal cyclic AMP production and phosphate uptake in OK cells. Both hPTH-(1-34) and hPTHrP-(1-34) stimulated intracellular cyclic AMP production to the same degree at concentrations between 10-10 and 10-7 M and inhibited phosphate uptake equipotently on a molar basis (27.5 .+-. 2.0 and 33.2 .+-. 1.2% inhibition at 10-7 M, respectively). Both exogenous addition of (Bu)2cAMP and endogenous stimulation of cAMP by forskolin inhibited phosphate uptake in a dose-dependent manner. Cyclic AMP production induced by either

with 1 ng of TNF.alpha./ml, whereas 1 .mu.M-RA was needed to observe the loss of PTH receptors. Combinations of RA and TNFA produced a greater effect than that of either agonist alone. The loss of PTH receptors was accompanied by a specific loss of PTH-stimulated cyclic AMP production. Preincubation with TNFA increased the basal plasminogen activator (PA) activity in the cells and decreased the amplitude of the response of PA activity to PTH compared with control cells. Furthermore TNFA decreased sensitivity to PTH (50% stimulation of PA activity with 0.1 nM-PTH in control cells versus 50% stimulation with 0.3 nM-PTH in TNF.alpha.-treated cells) . In contrast, TNF.alpha. pretreatment increased the amplitude of the response of PA activity to calcitonin, whereas sensitivity to calcitonin was not altered. These data are consistent with a specific down-regulation of PTH receptors in osteoblast-like UMR 106-06 cells after exposure to TNF.alpha. or RA. The loss of PTH receptors is accompanied by a decreased responsiveness to PTH, as measured with the PA system in these cells. A loss of PTH receptors could modulate PTH responses in osteoblasts, either in the local control of bone formation and resorption, or in pathological conditions such as humoral hypercalcaemia of malignancy.

L10 ANSWER 43 OF 54 MEDLINE
ACCESSION NUMBER: 90202767 MEDLINE
DOCUMENT NUMBER: 90202767 PubMed ID: 2318820
TITLE: ***Regulation*** of ***parathyroid*** ***hormone*** - ***related*** ***peptide*** gene expression by cycloheximide.
AUTHOR: Ikeda K; Lu C; Weir E C; Mangin M; Broadus A E
CORPORATE SOURCE: Department of Internal Medicine, Yale University, New Haven, Connecticut 06510.
CONTRACT NUMBER: AR-30102 (NIAMS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, ***(1990 Apr 5)*** 265 (10) 5398-402.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199005
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 19970203
Entered Medline: 19900503
AB A novel ***parathyroid*** ***hormone*** - ***related*** ***peptide*** (***PTHRP***) has been isolated from tumors associated with the syndrome of humoral ***hypercalcemia*** of malignancy. The human ***PTHRP*** gene appears to use multiple promoters and contains alternatively spliced 3' exons which give rise to three ***PTHRP*** mRNA classes, each bearing multiple copies of an AU motif that has been associated with mRNA instability. We report here that inhibition of protein synthesis leads to the super-induction of ***PTHRP*** mRNA expression in a number of human and rat cell lines. This phenomenon was found to reflect both an increase in the rate of ***PTHRP*** gene transcription and a stabilization of ***PTHRP*** mRNAs. The transcriptional mechanism appears to preferentially involve the activity of a short downstream promoter of the gene, which is presumed to be regulated by a labile repressor protein. Our findings indicate that both transcriptional and posttranscriptional mechanisms may be important control points in the regulation of ***PTHRP*** expression in normal and malignant cells.

L10 ANSWER 44 OF 54 MEDLINE
ACCESSION NUMBER: 91181414 MEDLINE
DOCUMENT NUMBER: 91181414 PubMed ID: 1964358
TITLE: Treatment of humoral ***hypercalcemia*** of malignancy in rats with ***inhibitors*** of carbonic anhydrase.
AUTHOR: Brown G M; Morris C A; Mitnick M A; Insogna K L
CORPORATE SOURCE: Yale University School of Medicine, Department of Internal Medicine, New Haven, CT 06510.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199203
ENTRY DATE: Entered STN: 19920410
Last Updated on STN: 19980206
Entered Medline: 19920326

AB The effects of transforming growth factor-alpha (TGF alpha) were determined on the ability of parathyroid hormone (PTH) or parathyroid hormone-related protein (***PTHrP***) to stimulate bone resorption and adenylate cyclase in vitro. Bovine PTH-(1-34) and human ***PTHrP*** -(1-34) were equipotent in their ability to stimulate bone resorption in neonatal mouse calvaria with maximal stimulation (2.9 and 2.8-fold increases in 45Ca release, respectively) at a concentration of 10 nM. Combinations of TGF alpha with bPTH-(1-34) or hPTHrP-(1-34) had additive effects on their ability to stimulate bone resorption when submaximal concentrations of the agonists were used. There was no evidence of synergism between TGF alpha bPTH-(1-34) or hPTHrP-(1-34) in their ability to stimulate bone resorption in vitro, nor was TGF alpha able to increase bone resorption induced by maximal concentrations of bPTH-(1-34) or hPTHrP-(1-34). TGF alpha potentiated the effects of either bPTH-(1-34) or hPTHrP-(1-34) on the stimulation of adenylate cyclase in osteoblast-like ROS 17/2.8 cells. These data indicate that TGF alpha has additive effects with submaximal concentrations of PTH or ***PTHrP*** on their ability to stimulate bone resorption which may be important in the pathogenesis of humoral ***hypercalcemia*** of malignancy.

L10 ANSWER 42 OF 54 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91354222 EMBASE
DOCUMENT NUMBER: 1991354222
TITLE: Specific down- ***regulation*** of parathyroid hormone (PTH) receptors and responses to PTH by tumour necrosis factor .alpha. and retinoic acid in UMR 106-06 osteoblast-like osteosarcoma cells.
AUTHOR: Schneider H.-G.; Allan E.H.; Moseley J.M.; Martin T.J.; Findlay D.M.
CORPORATE SOURCE: St Vincent's, Institute of Medical Research, 41 Victoria Parade,Fitzroy, Melbourne, Australia
SOURCE: Biochemical Journal, (1991) 280/2 (451-457).
ISSN: 0264-6021 CODEN: BIJOAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
016 Cancer
029 Clinical Biochemistry
033 Orthopedic Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Parathyroid hormone (PTH) and PTH-related protein (***PTHrP***) act via PTH receptors in bone to stimulate bone resorption. Bone resorption is also stimulated by certain cytokines, which are produced in bone and bond marrow. The effects of such cytokines on the PTH-receptor system were studied in the osteoblast-like osteosarcoma cell line UMR 106-06. 125I-labelled ***PTHrP*** -(1-84)-peptide bound specifically to the cells, and ***PTHrP*** (1-34) and (1-84) competed with equimolar affinity for binding to UMR 106-06 cells. The specific binding of 125I-***PTHrP*** -(1-84) could be completely blocked by PTH. Therefore 125I-***PTHrP*** -(1-84) bound to a classical PTH receptor in UMR 106-06 cells. Preincubation for 3 days with either tumour necrosis factor .alpha. (TNF.alpha.) or retinoic acid (RA) both decreased the specific binding of 125I- ***PTHrP*** -(1-84) to about 40% of control levels. These effects were specific for PTH binding, since there was little effect on 125I-salmon-calcitonin binding. Both TNF.alpha. and RA required 24 h exposure to cells to produce a measurable effect. The decrease in 125I-***PTHrP*** -(1-84) binding was due to a reduced number of binding sites, with little apparent change in affinity. Half-maximal effects were seen

PTHrp has recently been found in normal human cells, these studies suggest the possibility of ***PTHrp*** as a regulator or modulator of cardiovascular function.

L10 ANSWER 51 OF 54 MEDLINE
ACCESSION NUMBER: 89289616 MEDLINE
DOCUMENT NUMBER: 89289616 PubMed ID: 2737164
TITLE: ***PTHrP*** secretion is ***stimulated*** by CT and ***inhibited*** by CgA peptides.
AUTHOR: Deftos L J; Hogue-Angeletti R; Chalberg C; Tu S
CORPORATE SOURCE: Department of Medicine (Endocrine Division), University of California, San Diego.
SOURCE: ENDOCRINOLOGY, ***(1989 Jul)*** 125 (1) 563-5.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198908
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19890802
AB We studied the regulation of the secretion in vitro of the parathyroid hormone-related protein (***PTHrP***) associated with the ***hypercalcemia*** of malignancy by Chromogranin A (CgA)-derived peptides and by human calcitonin (CT) in the BEN human lung tumor cell line. The amino terminal peptide of CgA, CgA1-40, inhibited the secretion of ***PTHrP*** , whereas other peptides had no such effect. Human CT stimulated the secretion of ***PTHrP*** , whereas other hormones had no such effect. Both effects occurred in a dose-dependent manner. These studies reveal novel regulatory pathways among peptides and proteins that are commonly associated with each other and can have paracrine interactions. CgA may be processed at its multiple dibasic sites to peptides that regulate the secretion of its co-resident hormones, in this case ***PTHrP*** . In addition to a paracrine effect, CT may be clinically useful as a provocative agent for ***PTHrP*** secretion. Complex interactions are present among the calcium-regulating hormones and their associated proteins.

L10 ANSWER 52 OF 54 MEDLINE
ACCESSION NUMBER: 90201208 MEDLINE
DOCUMENT NUMBER: 90201208 PubMed ID: 2630297
TITLE: Renal vasodilatation and microvessel adenylate cyclase ***stimulation*** by synthetic parathyroid hormone-like protein fragments.
AUTHOR: Musso M J; Plante M; Judes C; Barthelmebs M; Helwig J J
CORPORATE SOURCE: Laboratoire de Physiologie Renale Rene Leriche, Universite Louis Pasteur, Strasbourg, France.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, ***(1989 Dec 19)*** 174 (2-3) 139-51.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199005
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 19980206
Entered Medline: 19900502
AB The ***hypercalcemia*** caused by malignancy factor, also called parathyroid hormone-related protein (***PTHrP***), exhibits most of the biological activities of parathyroid hormone (PTH) in kidney and bone. On the basis of the well-documented vascular action of PTH, we characterized the vasodilator action of human (h) ***PTHrP*** -(1-34) on a preparation of the isolated rat kidney, and its activity to stimulate adenylate cyclase in microvessels isolated from rabbit kidney cortex. Injection of sequential cumulative doses of hPTHrP-(1-34) into the

ISSN: 0531-5131. ISBN: 0-444-89489-6.
DOCUMENT TYPE: Article
LANGUAGE: English

L10 ANSWER 36 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:240508 BIOSIS
DOCUMENT NUMBER: PREV199344113708
TITLE: ***Regulation*** of the ***PTHrP*** gene and its protein products.
AUTHOR(S): Martin, T. J.; Moseley, J. M.; Gillespie, M. T.
CORPORATE SOURCE: St. Vincent's Inst. Med. Res., Univ. Melbourne, St. Vincent's Hosp., Fitzroy 3065 Australia
SOURCE: Cohn, D. V. [Editor]; Gennari, C. [Editor]; Tashjian, A. H., Jr. [Editor]. International Congress Series, (1992) No. 1003, pp. 25-35. International Congress Series; Calcium regulating hormones and bone metabolism: Basic and clinical aspects, Vol. 11.
Publisher: Excerpta Medica 305 Keizersgracht, PO Box 1126, Amsterdam, Netherlands.
Meeting Info.: 11th International Conference on Calcium Regulating Hormones Florence, Italy April 24-29, 1992
ISSN: 0531-5131. ISBN: 0-444-89489-6.
DOCUMENT TYPE: Article
LANGUAGE: English

L10 ANSWER 37 OF 54 MEDLINE
ACCESSION NUMBER: 92306900 MEDLINE
DOCUMENT NUMBER: 92306900 PubMed ID: 1319327
TITLE: ***Inhibition*** by human interleukin-1 alpha of ***parathyroid*** ***hormone*** - ***related*** ***peptide*** effects on renal calcium and phosphorus metabolism in the rat.
AUTHOR: Torring O; Turner R T; Carter W B; Firek A F; Jacobs C A; Health H 3rd
CORPORATE SOURCE: Endocrine Research Unit, Mayo Clinic Rochester, Minnesota 55905.
CONTRACT NUMBER: AR-35651 (NIAMS)
DK-07352 (NIDDK)
SOURCE: ENDOCRINOLOGY, ***(1992 Jul)*** 131 (1) 5-13.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920807
Last Updated on STN: 19920807
Entered Medline: 19920727
AB Humoral ***hypercalcemia*** of malignancy (HHM) is at least partly caused by tumor secretion of PTH-related peptide (***PTHrP***), but there is growing evidence for cosecretion with ***PTHrP*** of other bone-resorbing peptides, such as the cytokine interleukin-1 alpha (IL-1 alpha). Administration of ***PTHrP*** in vivo and in vitro generally mimics the actions of PTH itself, with increases in both resorption and formation of bone. However, bone in HHM is characterized by uncoupling of bone turnover, with increased resorption and decreased formation. We performed experiments to determine whether IL-1 alpha might alter the effects of ***PTHrP*** and produce uncoupling. Thus, we administered to 100-g male rats by sc osmotic minipumps synthetic ***PTHrP*** -(1-34) alone (2 micrograms/100 g/day), recombinant IL-1 alpha alone (1.5 micrograms/100 g/day), both peptides together at the previous doses, or vehicle only. We infused 5 groups of 12 rats each (***PTHrP*** , IL-1 alpha, ***PTHrP*** plus IL-1 alpha, ad libitum fed control, and controls pair-fed to the ***PTHrP*** plus IL-1 alpha group) for 14 days. At the end of the study, blood and urine were taken for chemical measurements, and tibias and femurs were harvested for histomorphometry and extraction of RNA from periosteal cells. As expected, ***PTHrP***

blocked by the G11 antibody. Depolarization with K+ or addn. of the voltage-dependent Ca2+ channel blocker verapamil had only marginal effects on [Ca2]i. Raised extracellular Ca inhibited release of ***PTHrp*** from the cells, and this inhibition was blocked by the G11 antibody. The virtually parathyroid-identical Ca2+ regulation of [Ca2+]i may mediate feedback control of ***PTHrp*** release from the cytotrophoblasts and thereby participate in the regulation of placental Ca2+ transport.

L10 ANSWER 34 OF 54 MEDLINE
ACCESSION NUMBER: 92337660 MEDLINE
DOCUMENT NUMBER: 92337660 PubMed ID: 1321618
TITLE: A parathyroid-related peptide induces transcaltachia (the rapid, hormonal ***stimulation*** of intestinal Ca2+ transport).
AUTHOR: Zhou L X; Nemere I; Norman A W
CORPORATE SOURCE: Division of Biomedical Sciences, University of California, Riverside 92521.
CONTRACT NUMBER: DK-09012-027 (NIDDK)
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ***(1992 Jul 15)*** 186 (1) 69-73.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208
ENTRY DATE: Entered STN: 19920904
Last Updated on STN: 19970203
Entered Medline: 19920814
AB PTH-related peptide (***PTHrP***) has been shown to be responsible for the hormonal ***hypercalcemia*** of malignancy. Previously, we demonstrated that both 1,25(OH)2-vitamin D3 and the N-terminal fragment of PTH (1-34) stimulates the rapid transport of Ca2+ (transcaltachia) in the perfused chick intestine. Since there is a sequence homology between these two hormones in the n-terminal fragment, in this study we examined the effect of ***PTHrP*** (1-40) on stimulation of transcaltachia in the perfused chick duodenum. The results indicate that the maximal stimulation of transcaltachia occurs at 50 pM ***PTHrP*** (1-40), and that the dose-response curve is biphasic in nature. Perfusion with 25 pM, 50 pM, 100 pM or 200 pM ***PTHrP*** (1-40) for 40 min increases the transport of Ca2+ in perfused intestine 1.8-, 3.0-, 2.4- and 1.6-fold, respectively. The response is rapid, occurring within 10 min of introduction of the ***PTHrP*** . The Ca2+ channel inhibitor nifedipine, which is known to abolish the transcaltachic effect elicited by 1,25(OH)2 vitamin D3, also inhibited the rapid transport of Ca2+ stimulated by ***PTHrP*** (1-40). The transcaltachic effect of ***PTHrP*** (1-40) may be mediated by a signal transduction pathway in which Ca2+ channels are activated.

L10 ANSWER 35 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:240512 BIOSIS
DOCUMENT NUMBER: PREV199344113712
TITLE: Human ***PTHrP*** gene transcription is ***stimulated*** by estrogen, EGF and TGF-beta.
AUTHOR(S): Gillespie, M. T. (1); Kiriyama, T. (1); Glatz, J. A. (1); Suva, L. J.; Fukumoto, S. (1); Heath, J. K. (1); Moseley, J. M. (1); Rodan, G. A.; Martin, T. J.
CORPORATE SOURCE: (1) St. Vincent's Inst. Med. Res., St. Vincent's Hosp., Melbourne 3065 Australia
SOURCE: Cohn, D. V. [Editor]; Gennari, C. [Editor]; Tashjian, A. H., Jr. [Editor]. International Congress Series, (1992) No. 1003, pp. 52-56. International Congress Series; Calcium regulating hormones and bone metabolism: Basic and clinical aspects, Vol. 11.
Publisher: Excerpta Medica 305 Keizersgracht, PO Box 1126, Amsterdam, Netherlands.
Meeting Info.: 11th International Conference on Calcium Regulating Hormones Florence, Italy April 24-29, 1992

mediate the bone-resorptive action of certain hormones, we examined the effect of ***PTHrP*** on prostaglandin E2 (PGE2) secretion by human osteoblast-like cells. There was low-level basal secretion of PGE2 by Saos-2 cells (8.1 +/- 0.6 pg/ml). Using four different preparations of ***PTHrP*** , it was observed that with increasing peptide length, from 36 to 141 amino acids, a significant increase in efficacy for PGE2 release was seen in these cells. All forms of ***PTHrP*** were agonists for PGE2 release, with effects seen at concentrations as low as 10(-12) M in 48 h conditioned media. The amino terminus of the molecule appeared critical for this effect since the truncated derivative ***PTHrP*** -(7-34) did not induce significant PGE2 secretion. However, the influence of peptide length could not be explained by differential activation of adenylate cyclase since [Tyr36] ***PTHrP*** -(1-36)amide was equipotent to the longest peptide preparation, ***PTHrP*** -(1-141), in stimulating cyclic AMP accumulation in the Saos-2 cells. In contrast, ***PTHrP*** -(1-141) was significantly more effective than [Tyr35] ***PTHrP*** -(1-36)-amide in inducing a rise in cytosolic calcium. Further, this effect was noted at concentrations lower than those that caused significant cyclic AMP accumulation in the Saos-2 cells. ***PTHrP*** -(1-141) induced the release of PGE2 from primary human bone cell cultures to levels entirely comparable to those seen in the Saos-2 cells. ***PTHrP*** -(1-141) also induced PGE2 release by cultured fetal rat long bones at 72 h. We conclude that the carboxy-terminal region of ***PTHrP*** has important effects on cellular signal transduction pathways and on the release of a potent bone-active cytokine, PGE2.

L10 ANSWER 31 OF 54 MEDLINE
ACCESSION NUMBER: 92118035 MEDLINE
DOCUMENT NUMBER: 92118035 PubMed ID: 1310016
TITLE: Tumor necrosis factor alpha ***inhibits*** the ***stimulatory*** effect of the parathyroid hormone-related protein on cyclic AMP formation in osteoblast-like cells via protein kinase C+.
AUTHOR: Blind E; Knappe V; Raue F; Pfeilschifter J; Ziegler R
CORPORATE SOURCE: Department of Internal Medicine I-Endocrinology and Metabolism, University of Heidelberg, Germany.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ***(1992 Jan 15)*** 182 (1) 341-7.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199202
ENTRY DATE: Entered STN: 19920308
Last Updated on STN: 19970203
Entered Medline: 19920218
AB Tumor necrosis factor alpha (TNF alpha) and parathyroid hormone-related protein (***PTHrP***) are both factors that have been implicated in the mechanism of ***hypercalcemia*** of malignancy. In this study we investigated the effect of TNF alpha on the ***PTHrP*** -stimulated accumulation of intracellular cyclic AMP in osteoblast-like cells. In the clonal cell line Saos-2 and in primary cell cultures from fetal rat calvaria, ***PTHrP*** -stimulated accumulation of cAMP was time- and dose-dependently inhibited by exposure to TNF alpha. Significant inhibition occurred at concentrations as low as 2 x 10(-12) M and was maximal at 1 x 10(-9) M. Inhibition was observed after 6 h and was maximal after 18 h. Inhibition by TNF alpha was probably mediated by protein kinase C, since the phorbol ester PMA mimicked the effect of TNF alpha, and the protein kinase C inhibitor H-7 completely abolished the effect of TNF alpha. In conclusion, these observations suggest a possible mechanism by which TNF alpha may modulate the effect of ***PTHrP*** on osteoblast function in the syndrome of humoral ***hypercalcemia*** of malignancy.

L10 ANSWER 32 OF 54 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92245313 EMBASE

bone cells.

L10 ANSWER 26 OF 54 MEDLINE
ACCESSION NUMBER: 93315608 MEDLINE
DOCUMENT NUMBER: 93315608 PubMed ID: 8325957
TITLE: The combined effect of tumor-produced parathyroid hormone-related protein and transforming growth factor-alpha ***enhance*** ***hypercalcemia*** in vivo and bone resorption in vitro.
AUTHOR: Guise T A; Yoneda T; Yates A J; Mundy G R
CORPORATE SOURCE: Department of Medicine, University of Texas Health Science Center, San Antonio 78284-7877.
CONTRACT NUMBER: AR-39529 (NIAMS)
CA-40035 (NCI)
DE-08569 (NIDCR)
+
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, ***(1993 Jul)*** 77 (1) 40-5.
Journal code: 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199308
ENTRY DATE: Entered STN: 19930820
Last Updated on STN: 20000303
Entered Medline: 19930806
AB Humoral ***hypercalcemia*** of malignancy is a multifactorial syndrome caused by the action of tumor-produced factors on target organs of bone, kidney, and intestine to disrupt normal calcium homeostasis. Although parathyroid hormone-related protein (***PTHrP***) plays an integral role in the syndrome, tumors also produce other hypercalcemic factors, such as transforming growth factor-alpha (TGF-alpha), which may modulate the effects of ***PTHrP*** . In order to determine if the effects of ***PTHrP*** on calcium homeostasis can be modulated by TGF-alpha, we have used a human squamous cell carcinoma cell line (RWGT2) which produces ***PTHrP*** alone and Chinese hamster ovarian (CHO) cells expressing only transfected human TGF-alpha complementary DNA (CHO/TGF-alpha). We studied the effects of these tumors on calcium homeostasis in nude mice bearing both tumors or each tumor alone. Whole blood ionized calcium concentrations (mean +/- SEM in mmol/L) were significantly higher in mice bearing both RWGT2 and CHO/TGF-alpha tumors (3.11 +/- 0.06, $P < 0.05$) when compared with mice bearing either RWGT2 alone (2.02 +/- 0.06), CHO/TGF-alpha alone (1.42 +/- 0.01), or RWGT2 and nontransfected CHO tumors (1.86 +/- 0.01). This enhanced effect was also observed using continuous ***PTHrP*** -(1-34) infusion (2 micrograms/day) in mice bearing CHO/TGF-alpha tumors. In addition, tumor cell conditioned media was tested for bone resorbing activity in organ cultures of fetal rat long bones previously incorporated with 45calcium (45Ca++). Conditioned medium at 0.1% (vol/vol) from either RWGT2 or CHO/TGF-alpha had no bone resorbing activity over control (%45Ca++ release, mean +/- SEM; control 23 +/- 1, RWGT2 19 +/- 1, CHO/TGF-alpha 23 +/- 1). However, the combination of 0.1% conditioned medium from RWGT2 and CHO/TGF-alpha significantly increased bone resorption (53 +/- 2, $P < 0.05$). These data demonstrate that the hypercalcemic effects of tumor-produced ***PTHrP*** are enhanced by TGF-alpha and that this effect may be due to increased bone resorption.

L10 ANSWER 27 OF 54 MEDLINE
ACCESSION NUMBER: 92212903 MEDLINE
DOCUMENT NUMBER: 92212903 PubMed ID: 1313566
TITLE: Expression cloning of a common receptor for parathyroid hormone and ***parathyroid*** ***hormone*** - ***related*** ***peptide*** from rat osteoblast-like cells: a single receptor ***stimulates*** intracellular accumulation of both cAMP and inositol trisphosphates and increases intracellular free calcium.
AUTHOR: Abou-Samra A B; Juppner H; Force T; Freeman M W; Kong X F;

Entered Medline: 19950316

AB PTH is a peptidic hormone which regulates blood calcium level. The PTH gene has been characterized and has 3 exons and 3 introns. PTH is synthetized as a precursor (pre-pro-PTH). The sequence "pre" is the signal peptide. The role of the sequence "pro" is still unknown. Main factors which regulate PTH synthesis are the level of extra-cellular calcium, vitamin D, and to a lesser extent steroid hormones. Calcium is the main factor influencing PTH secretion. Very recently, a "calcium sensor" has been purified and cloned. It is present on the membrane of parathyroid cells and some specific agonists of these receptors are already purified and could modulate PTH secretion. PTH-RP is responsible of ***hypercalcemia*** of tumors and has structural homologies with PTH. But, whereas PTH is only secreted by parathyroid cells, PTH-RP is synthetized by several different cell types and seems to act as an autocrine factor. Two major questions are still unanswered: 1) Is there only one receptor for PTH and PTH-RP? Some studies concluded that there are probably at least 2 different receptors, 2) And what is the role of PTH-RP? Many effects have already been published: pth-RP is involved in placental physiology, keratinocyte differentiation, or vascular smooth cell relaxation.

L10 ANSWER 17 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:240788 BIOSIS
DOCUMENT NUMBER: PREV199497253788
TITLE: Transcription ***regulation*** of the ***parathyroid*** ***hormone*** - ***related*** ***peptide*** (***PTHrP***) by the Wilms tumor (WT1) tumor suppressor protein.
AUTHOR(S): Fleischhacker, M.; Ejima, E.; Prager, D.
CORPORATE SOURCE: Cedars Sinai Med. Cent., Dep. Endocrinol., 3008 Davis Bldg., 8700 Beverly Blvd., Los Angeles, CA 90048 USA
SOURCE: Journal of Cancer Research and Clinical Oncology, (1994) Vol. 120, No. SUPPL., pp. R109.
Meeting Info.: 21st National Cancer Congress of the German Cancer Society Hamburg, Germany March 7-11, 1994
ISSN: 0171-5216.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 18 OF 54 MEDLINE
ACCESSION NUMBER: 93293973 MEDLINE
DOCUMENT NUMBER: 93293973 PubMed ID: 8514854
TITLE: A vitamin D analogue (EB1089) ***inhibits*** ***parathyroid*** ***hormone*** - ***related*** ***peptide*** production and prevents the development of malignancy-associated ***hypercalcemia*** in vivo.
AUTHOR: Haq M; Kremer R; Goltzman D; Rabbani S A
CORPORATE SOURCE: Department of Medicine, McGill University.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, ***(1993 Jun)*** 91 (6) 2416-22.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930806
Last Updated on STN: 19950206
Entered Medline: 19930721

AB We have examined the effects of 1,25 dihydroxyvitamin D3 (1,25[OH]2D3) and a low calcemic analogue EB1089 on ***parathyroid*** ***hormone*** - ***related*** ***peptide*** (***PTHRP***) production and on the development of ***hypercalcemia*** in Fischer rats implanted with the Leydig cell tumor H-500. Leydig cell tumors were implanted subcutaneously into male Fischer rats, which received constant infusions intraperitoneally of either 1,25(OH)2D3 (50-200 pmol/24 h), EB1089 (50-400 pmol/24 h), or vehicle for up to 4 wk. A control group of animals received

ISSN: 0893-3952.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 10 OF 54 MEDLINE
ACCESSION NUMBER: 95266471 MEDLINE
DOCUMENT NUMBER: 95266471 PubMed ID: 7747629
TITLE: In vivo evidence for progressive activation of ***parathyroid*** ***hormone*** - ***related*** ***peptide*** gene transcription with tumor growth and ***stimulation*** of osteoblastic bone formation at an early stage of humoral ***hypercalcemia*** of cancer.
AUTHOR: Yamato H; Nagai Y; Inoue D; Ohnishi Y; Ueyama Y; Ohno H; Matsumoto T; Ogata E; Ikeda K
CORPORATE SOURCE: Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Japan.
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, ***(1995 Jan)*** 10 (1) 36-44.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950621
Last Updated on STN: 19950621
Entered Medline: 19950612
AB The present study was undertaken to clarify in vivo the temporal profile of ***parathyroid*** ***hormone*** - ***related*** ***peptide*** (***PTHRP***) gene expression as well as bone histomorphometric features as a function of tumor growth, using an athymic rat model associated with humoral ***hypercalcemia*** of malignancy (HHM). Tumor-bearing animals exhibited ***hypercalcemia*** , hypophosphatemia, and increased circulating levels of ***PTHRP*** , and died within 3 weeks. Steady-state ***PTHRP*** mRNA levels and the transcription rate of ***PTHRP*** gene in the tumors were markedly increased with tumor growth. RNAse mapping analysis revealed that both upstream and downstream promoters of the human ***PTHRP*** gene were utilized in the tumors and became progressively activated with time. Bone histomorphometric analysis showed that osteoclastic bone resorption was progressively increased throughout the course, whereas osteoblastic bone formation was stimulated more than 2-fold at a very early stage (day 6 after tumor implantation) and then markedly suppressed thereafter on day 12 and day 18 compared with age-matched control animals. These results provide in vivo evidence that ***PTHRP*** gene transcription is progressively activated with tumor growth and that activation of osteoblasts does occur at a very early phase of HHM syndrome in contrast to the marked suppression of bone formation at later stages.

L10 ANSWER 11 OF 54 MEDLINE
ACCESSION NUMBER: 95214342 MEDLINE
DOCUMENT NUMBER: 95214342 PubMed ID: 7535368
TITLE: Simultaneous production of parathyroid hormone-related protein (***PTHrP***) and granulocyte colony-***stimulating*** factor (G-CSF) in lung cancer patients with ***hypercalcemia*** and leukocytosis.
AUTHOR: Sakamoto A; Katakami H; Mukae H; Taniguchi H; Maki H; Ashitani J; Ihi T; Dohtsu Y; Matsukura S
CORPORATE SOURCE: Third Department of Internal Medicine, Miyazaki Medical College, Japan.
SOURCE: NIHON KYOBU SHIKKAN GAKKAI ZASSHI. JAPANESE JOURNAL OF THORACIC DISEASES, ***(1995 Jan)*** 33 (1) 34-8.
Journal code: 7505737. ISSN: 0301-1542.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals

effect of transforming growth factor-alpha (TGF-alpha), which is another tumoral product secreted by certain ***hypercalcemia*** -associated tumors, on NaPiT and the TGF-alpha-induced modulation of the response to ***PTHrP*** or PTH. TGF-alpha caused a 30% stimulation of NaPiT, which remained stable from 6 to 24 h, by a cAMP-independent mechanism. In contrast, TGF-alpha attenuated cAMP production stimulated by PTH, ***PTHrP*** -(1-34), or ***PTHrP*** -(1-141). ***PTHrP*** or PTH did not further increase NaPiT in TGF-alpha-treated cells. These results indicate that NaPiT, a possibly important function of osteoblastic cells, was similarly affected by PTH and ***PTHrP*** . TGF-alpha increased NaPiT and modulated in a similar way the effects of both PTH and ***PTHrP*** .

L10 ANSWER 40 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1992:6481 BIOSIS
DOCUMENT NUMBER: BA93:6481
TITLE: ***REGULATION*** OF PARATHYROID HORMONE-RELATED PROTEIN PRODUCTION IN HUMAN CANCER CELLS.
AUTHOR(S): KASONO K
CORPORATE SOURCE: DEP. MED. II, TOKYO WOMEN'S MED. COLL.
SOURCE: J TOKYO WOMEN'S MED COLL, (1991) 61 (8), 611-618.
CODEN: TJIZAF. ISSN: 0040-9022.
FILE SEGMENT: BA; OLD
LANGUAGE: Japanese
AB Previously, we reported that human cancer cells (EC-GI and T3M-1) produced parathyroid hormone-related protein (***PTHrP***) and developed ***hypercalcemia*** in the tumor-bearing mice. We investigated the regulation of ***PTHrP*** production in these cancer cells. Human esophageal cancer cells (EC-GI) or submandibular cancer cells (T3M-1) were cultured with 12-o-tetradecanoylphorbol-13-acetate (TPA), glucocorticoids, calcitonin, indomethacin, 17.beta.-estradiol or testosterone for 2 days. Northern blot analysis of total or poly (A)+ RNA from these cells were performed. ***PTHrP*** secreted into the medium was determined by adenylate cyclase-stimulated activity or radioimmunoassay for N-terminal human ***PTHrP*** (1-34). Preliminary studies revealed that ***PTHrP*** gene was mainly expressed in the logarithmic growth phase. Therefore, we used the cells in that cell density. TPA (10-9 M) stimulated ***PTHrP*** gene expression in EC-GI cells. TPA (2 .times. 10-8 M) also stimulated ***PTHrP*** production. Hydrocortisone (10-8 M) inhibited ***PTHrP*** mRNA levels in EC-GI and T3M-1 cells and also inhibited dose-dependently ***PTHrP*** production in EC-GI cells. Another glucocorticoid, prednisolone (10-7 M) inhibited ***PTHrP*** production. Calcitonin had no effect on ***PTHrP*** production. When hydrocortisone and calcitonin were simultaneously added, calcitonin did not affect hydrocortisone-induced inhibition of ***PTHrP*** productin. Indomethacin, 17.beta.-estradiol and testosterone had no effects on ***PTHrP*** production. We have demonstrated that glucocorticoids inhibited directry ***PTHrP*** gene expression and production in cancer cells associated with ***hypercalcemia*** . These in vitro data suggest that the combined therapeutic effects of glucocorticoids and calcitonin are partly due to inhibition of ***PTHrP*** production in addition to the inhibitory effects on osteoclast.

L10 ANSWER 41 OF 54 MEDLINE
ACCESSION NUMBER: 92154912 MEDLINE
DOCUMENT NUMBER: 92154912 PubMed ID: 1786699
TITLE: Effects of transforming growth factor-alpha on parathyroid hormone- and parathyroid hormone-related protein-mediated bone resorption and adenylate cyclase ***stimulation*** in vitro.
AUTHOR: Rosol T J; Merryman J I; Nohutcu R M; McCauley L K; Capen C C
CORPORATE SOURCE: Department of Veterinary Pathobiology, College of Veterinary Medicine, Ohio State University, Columbus 43210.
SOURCE: DOMESTIC ANIMAL ENDOCRINOLOGY, ***(1991 Oct)*** 8 (4) 499-507.
Journal code: 8505191. ISSN: 0739-7240.